British Journal of Medicine & Medical Research
1(4): 239-305, 2011

SCIENCEDOMAIN *international*
www.sciencedomain.org

Role of Zinc in an Organism and Its Influence on Processes Leading to Apoptosis

M. A. Orlova[1*] and A. P. Orlov[2]

[1]M.V. Lomonosov Moscow State University, Faculty of Chemistry, 1/3, Leninskiye Gory, Moscow 119899, RUSSIA.
[2]N.I. Pirogov Russian State Medical University, 1 Ostrovityanova St., Moscow 117997, RUSSIA.

Review Article

Received 19th June 2011
Accepted 5th July 2011
Online Ready 28th July 2011

ABSTRACT

This review brings together and analyzes the problem of zinc effects on the body through apoptosis, also affecting the latest data in the study of process itself apoptosis. Also, the possibility of using zinc and its derivatives and its complexes in cancer treatment are discussed. The review also focuses on the biochemical problems that lead to various diseases occurring in conditions of excess or deficiency of intracellular zinc. Review includes more than 300 references and contains research over the past ~ 15 years, focusing on the latest data.

Keywords: Zinc; apoptosis; metallothioneins; superoxise dismutase; zinc fingers; angiotensin-converting enzyme; magnetic isotope effect; zinc-complex; zinc-transporters;

**Corresponding author: Email: orlova.radiochem@mail.ru;*

CONTENT

Sl. No.	Title	Page No.
	Abbreviations	240
1.	Insight into zinc functions in an organism.	241
2.	Modern understanding of apoptosis process: 2.1 Main ways of apoptosis realization; 2.2 Concentration-dependent effects of zinc ions on apoptosis.	243
3.	Uptake, storage and transport of zinc in an organism: 3.1 Metallothioneins, zinc fingers, zinc transporters, angiotensin-converting enzyme.	254
4.	Antioxidant properties of zinc: 4.1 Cu/Zn-superoxide dismutase; Zn and hydrogen peroxide; 4.2 Zn and caspase cascade, Zn and NO;	261
5.	Zinc effects on brain cells apoptosis: 5.1 Alzheimer's disease; 5.2 Zn and lateral amyotrophic lateral sclerosis (ALS);	270
6.	Anti-inflammatory properties of zinc. Zinc effects on immune response of an organism.	276
7.	Relationship of biological effects of zinc and other metals.	277
8.	Zinc complex in conditions of ionizing and UV irradiation 8.1 Photodynamic Therapy;	280
9.	Zinc magnetic isotopic effect in biochemistry	283
10.	Conclusion	284
	Acknowledgement	284
	References	284

ABBREVIATION

ALS – amiotrophic lateral sclerosis; FALS – family ALS; AD – Alzheimer`s disease; Aif – apoptosis-induce factor; ACE – angiotensin-converting enzyme; AMPK – AMP-activated proteinkinases; AMPA-Ca-A/K – 2-amino - 3 (3 – hydroxy - 5methyl isoksazol – 4 - yl) methyl isopropionic acid / kainate channels; A2M – α-macro globulin; AcSDKP – N-acetyl –Ser-Asp-Lys-Pro; AT1, AT2 – angiotensin receptor 1 and 2; AE – airways epithelium; AP-1, C-mys, C-fos, Nurr, GATA4, NF-AT, NF-jB, NF-ηB, NF-κB – transcripton factors; AML – acute myeloid leukemia; BCA2 – breast cancer associated gene 2; BPDS – batofenantrolin sulfonic acid; CytC – cytochrome C; CSS – coper chaperon for SOD1; CEES – 2-chloroethyl ethyl sulfide; CAT – catalase; GCL – glutamate cysteine ligase; CSF – cerebro-spinal fluid COLD – chronic obstructive lung disease; DFT – density functional theory; DMT – divalent metal ions transporter; DNA-Pol – DNA-polymerases; DDC – diethyldithiocarbamate; ESI-MS – electrospray ionisation mass spectrometry; FasR, Fas-L, TNFR, TRAILR – region cell death receptors; GPI-ase – GPI-anchor protein released; G6PD – glucose-6-phosphate dehydrogenase; Gpx – glutathion peroxidase; Gsr – glutathion reductase; GSSG/GSH – oxidized/reduced glutathione; Glu/GO – glucose/glucose oxidase; Grx – glutathion reduxin

Hsp90, Hsc70 – shaperons; Hes-1 – transcription factor of helix-loop-helix family; HIF – hipoxia-inducible factor responsible for the reaction to the lack of oxygen; ICE – interleukin-1β-converting enzyme; IL-1, IL-6, IL-12, IFN-γ – cytokins; ICDH – isocitrate dehydrogenase JAK-STAT – signalling pathway; JNK-AP-1 – signalling pathway; Keap-1 – Kelh-like ECH-associated protein 1 – cytoplasmatic repressor of transcription factor Nrf2. It inhibits Nrf-2-translocation to the nucleus; MT – metallothioneins; MTF-1 – transcription factor 1; MAPK – mitogen-activated protein kinases; MPTP – 1-methyl – 4 – phenyl – 1,2,3,6 – tetrahydro pyridine; NAC – N-acetyl-L-cysteine; NOS – NO-synthases; NAD+/NADH – oxidized/reduced nicotinamid adenine dinucleotide (P - phosphate); NOX – NADH-oxidase; NGF – nerve growth factor; NMDA – N-methyl-D-aspartate; NSC – neuronal stem cells; Nrf-2 –Keap-1 – signalling system; PBMC – peripheral blood mononuclear cells; PDTC – pyrrolidine dithiocarbamate; PD – Parkinson`s disease; PTD – transduction protein domains; PGC-1α – transcriptional coactivator steroid and nuclear receptors, s.c. mitochondrial coach pVHL – von Hippel-Lindau tumor suppressor; PCK – protein kinase C; PCA – protein kinase A; PARP – poly(ADP-ribose)polymerase; PARG – poly(ADP-ribose)glycohydrolase; ROS – reactive oxidative speciaes; RNS – reactive nitrosospeciaes; RNI – reactive nitrosointermediates; R-Smad – receptor-regulated transcription factors; RAS – renin-angiotensin system; PRE cells – retinal pigment epithelian cells; Smac/Diablo – second mitochondrial derived activator of caspase/direct IAP-binding protein with a low pI; SL1 – ribosome gene transcription activator; SNP – sodium nitroferricyanide; SNAP – S-nitroso-N-acetyl penicillamine; Sirt-1 – sirtuin -1; SMP30 – human marker protein of ageing 30; TPEN – N,N,N`,N`-tetrakis(2-pyridyl-methyl)ethylenediamine; TNF – tumor necrosis factor; TDAG51 – Fas-regulatory gene; TCR – T-cell receptor; TGF-β – transforming growth factor β (signalling pathway); UBF – upstream binding factor; USM – ubiquitin-binding motif; Wnt – signalling pathway; XIAP – X-chromosome inhibitor of apoptosis; ZEN – Zn-riched neurons.

1. INSIGHT INTO ZINC FUNCTIONS IN AN ORGANISM

Zinc is a microelement and presents in all organs, tissues, fluids in the organism and ~95% of zinc is intracellular one. Almost 70% of total amount zinc in the organism is in erythrocytes being a part of an enzyme carboanhydrase. Zinc also is a constituent of transcription factors, which regulate activity of genome in hemopoietic cells**.** The highest zinc concentrations are in the brain and pancreatic cells (Kozlowski et al., 2009). From 3 to 10 % of total mammalian proteins bind zinc as an important cofactor necessary for folding, conformational changes and activity. More than 300 enzymes include zinc in their structure (Parkin, 2004) (according to recent data, this value is much more (Maret, 2010). Zinc is essential for functioning of DNA- and RNA-polymerases, that control the process genetic information transduction and, as a consequence, biosynthesis of proteins. Zinc is also a constituent of active center of angiotensin-converting enzyme (ACE) that has a wide range of activities in the organism, including neurotransmitting, regulation of the blood pressure and reproduction (Defenini et al., 1983; Corvol et al., 2004; Ehlers et al., 1989). Zinc is a cofactor of key enzymes of biosynthesis of heme that is a prosthetic group of hemoglobin; it is also a cofactor of endonucleases and participates in controlling of the cell cycle etc. It is crucial, that zinc is a cofactor of antioxidant enzyme, namely, Cu,Zn–superoxide dismutase (SOD), that controls oxidative stress and thereby apoptosis, i.e. programmed cell death. Due to this ability, zinc is an antioxidant of reparative action.

In general, it may be told that the main function of zinc is a total control of proper conformational state of many constituents of the organism and components of biochemical processes.

It is possible to suggest (Oteiza et al., 2005) several functions of zinc in biological systems:

1. Structural component of a large amount of proteins and participation in catalysis;
2. Participation in protection of an organism;
3. Structural, regulatory and antioxidant functions of membrane-bound Zn; the latter also serves as a pool of readily available Zn;
4. Zn is an essential component to maintain proper structure of cytoskeleton;
5. Zn plays an important role in cell signaling. Zn-binding proteins constitute almost half regulatory transcription factors in the human genome (Tapler et al., 2001).

However, free or labile zinc may be very toxic for mammalian cells (Frederickson et al., 2005). Recent studies show that concentration of zinc ions in a cytosole has constant value and is maintained with participation of zinc-binding proteins and Zn-transporters that prevent increasing of cytosolic zinc concentration. This is a buffering property of zinc. In non-stationary conditions all zinc-binding molecules act in co-ordination with each other to maintain initial (non-toxic) concentration. This process is named as zinc quenching. It is considered (Colvin et al., 2010) that this quenching represents the Zn-signaling pathway that is tightly linked to mechanisms of binding and releasing of zinc by metallothioneins.

It is necessary to distinguish functions of fixed and labile pool of zinc in the organism (Dumay et al., 2006). The fixed state implies the zinc content in metalloenzymes and “zinc fingers” proteins, which possess the same motif, containing histidine and cysteine residues to which zinc is bound. The major zinc-binding proteins are DNA-binding transcription factors which are responsible for identification of DNA sites by proteins. In these proteins Zn forms the structure helix-turn-helix (see Chapter 3). Turnover of zinc responsible for cell metabolism and gene expression proceeds slowly (Palmiter et al., 1996). 10-15% of total zinc is labile one and it differs from the fixed zinc due to its presence in certain tissues and tissue regions. In cells zinc is localized in membranous organelles (vesicles, Golgi apparatus). Its excessive release from such reserves threatens cytoplasmic enzymes its toxicity (Ward et al., 2000). Ligands-chelators (Frederickson, 2003), ionophores (Ho et al., 2004; Ding et al., 2008, 2009) are used to bind the excessive labile zinc.

Influence of zinc on functions of an organism is so great and diverse, so that its deficiency even may increase susceptibility to alcoholism (Nelson et al., 2002) and underlie the pathology of the skin due by zinc deficiency, causing apoptosis (Wilson et al., 2006).

It is necessary to note that deficiency as well as excess of zinc suppresses expression of such proteins as S-glutathiol carboanhydrase, myosine light chain 3, heat shock protein 20 and a protein, that binds fatty acids in the heart (Grider et al., 2007), what negatively influences functions of sceletal muscles. On this basis an opinion is proposed that consumption of even pharmacological doses of zinc may be harmful. In general, the toxicity of zinc for animals and human is low, because it is not accumulated is excessive influx and is removed from the body.

Since zinc may not be accumulated in the organism, its permanent consumptions with food, in particular, with meat (Solomons, 1988.), sea products, dairy products, groats and nuts (Dreosti, 1993) are necessary. Zinc may not be provided with vegetables because most of

them contain a large amount of phytate, the zinc chelator, which inhibits zinc assimilation (Arcenault et al., 2003).

As usual the main problem dealing with zinc and leading to pathologies is its insufficient intake by an organism due to its deficiency in the food (often because of simultaneous presence of complex forming compounds), water and soil in a region. Deregulation in zinc homeostasis leads to zinc deficiency or its specific accumulation in toxic concentrations. There is a concept of Zn-deficient territories, and living at these territories threatens with zinc deficiency in nutrition with corresponding pathological consequences, which were described in details in medical literature. In particular, this concerns impairment in eye vision deterioration and immunodeficiency. The former is a result of lack of activation by zinc of retinol dehydrogenase that participates in light quantum perception and also linked with zinc participation in vitamin A conversion (in the liver) to the form proper for light perception and the vitamin A transfer from the liver to eye retina.

The zinc deficiency is particularly characteristic for elderly and old ages, that is dependent on changes (often with direct decreasing) of type of nutrition, that leads to decreasing of zinc concentration in the body and also with usage of drugs (in particular, diuretic), leading to fast excretion of zinc from the body. Thus, some problems characteristic for old age may be resulted from zinc deficiency in the organism. Also, incorrect zinc turnover may lead to increasing of its cytotoxic labile fraction, what strengthen zinc disbalance.

Especially it is necessary to note that during malignant (not benign) tumor growth zinc concentration in the blood is decreased and this may be used in early diagnostics of cancer. Zn may influence processes in the organism indirectly through numerous factors, which by one way or another are linked with cell apoptosis, so, the zinc homeostasis is one of the signaling systems of apoptosis (and associated with it oncogenesis). So, complex interrelationships of apoptotic events with functional peculiarities of zinc behavior in the body are of particular interest of this review. Also an attempt to consider several signaling ways, where zinc ions may take part, was made.

2. MODERN UNDERSTANDING OF APOPTOSIS PROCESS

Apoptosis is one of types of cell death, participating in a set of biological cycles during development of biological tissue, its degeneration or reparation. It may be caused by numerous extracellular and intracellular factors and here several metals such as Zn, Ca and Fe (though a list of important microelements was expanded in the last time (Rana, 2008) play a most important role. Intracellular zinc is described as the apoptosis inhibitor, but, on the contrary, its exhaustion in the organism (or its deficiency in a food) induces death of many cell lines (Sunderman, 1995; Truong-Tran et al., 2000). Cells possess perfect control mechanism to maintain metals concentrations at proper levels by way of coordinating and regulating process of their consumption, transformation and storage (Maret et al., 2010; Maret, 2011; Maret and Li, 2009). Such a control of ions consumption and storage is strongly regulated by feed-back system with participation of regulatory proteins and metal shaperones.

2.1 Main Ways for Apoptosis Realization

It is known, that apoptosis, in difference from necrosis, is a programmed function of the organism, which is necessary for its existence. A biological role of apoptosis is to maintain a balance between cell proliferation and death. In the genome of each cell there are genes

which react to action of inductors and inhibitors of apoptosis and, the latters are, respectively, activators and blockers of this process. Disruption of apoptosis process is a basis for development of a number of diseases, including tumors.

Initially there should be a signal to a cell to induce apoptosis, for example, through activation of p53 gene as a result of DNA damage, impact of radiation, cytotoxic agents, glucocorticoids, disruption of regulation by cytokines, shortening up to critical level of telomers etc. This way is controlled by mitochondria (Brunelle et al., 2009) and it causes activation of caspase-9 at a final stage (Vladimirskaya, 2007). Another known signaling pathway proceeds through activation of cell death receptors, which include, in particular: Fas-R (also named as CD95 or APO1), TRAIL-R1/R2, TNF-R1/R2 (Filchenkov, 2009; Fulda et al., 2010) and TNF-R1/R2 (Fulda et al., 2010; Wyllie, 2010; Portt et al., 2010), and the pathway is finished by activation of inductor caspase-8 (-2 or -10). Specific protein Fas-L - the ligand of Fas-receptor – belongs to the family of TNF-like cytokines (Suda et al., 1994). FasR is expressed on the surface of all cell types of the organism, especially upon their activation. Fas-L is predominantly expressed on activated lymphocytes ($CD8^+$ T-lymphocytes, in less extent $CD4^+$ T-lymphocytes, NK-cells) and cells of some organs (Sertolli cells, cornea epithelium, retina, keratinocytes). FasR appears on the membrane of T-lymphocytes during their transition from the rest phase to presynthetic phase of cell cycle, and this is accompanied by activation of protein kinase C and transcription factors NF-AT, AP-1 (Patricia et al., 2000) Nur77 and induction of transcription of Fas-regulatory gene (TDAG51).

Inductor caspases (caspases 2,8,9,10) are able to activate effector (or killer) procaspases (caspases 3,6,7), which being activated start cell destruction. Caspases are cysteine proteases and split in proteins peptide bonds formed with participation of asparagine residues. After that changes visible with electron microscopy take place: consolidation of chromatine, its condensation, changes of cytoplasm. Further decomposition of the nucleus to discrete fragments, which are surrounded by cytoplasm with not damaged cell membrane – apoptotic bodies - is observed (Lushnikov et al., 1987, 2001). Then these apoptotic bodies are degraded by macrophages, dendrite or endothelial cells. Receptors which recognize phosphatidylserine, appearing on external layer of membrane of apoptosis bodies, take part in phagocytosis. At this stage cytochrome C (CytC) participates in the process of apoptosis controlling, because an oxidized form of CytC after releasing from mitochondria may treat by peroxide the phosphatidylserine at the internal membrane (Jiang et al., 2003; Kagan et al., 2004). This oxidized form of phosphatidylserine, seemingly, is exported predominantly into external part of the cell membrane, where it provides a signal "eat me" to phagocytes. Phagocytes produce an inhibitory cytokine – transforming growth factor β (TGFβ) (Vladimirskaya, 2002, Grigoriev et al., 2003).

Such apparently simple and clear ways of apoptosis are performed, however, through numerous channels and mediated by many stages, which have not been elucidated yet.

The way from activation of p53 to caspase 9 runs through activation of proapoptotic genes belonging to Bcl-2 family (Bax, Bid, Bak) (Rinkenberger et al., 1997; Brunelle et al., 2009). 16 genes from this family were cloned (mapped at chromosome 18 in human). They are united by the presence of, at least, one of 4 conservative amino acid sequences characteristic for Bcl-2 (domains BH1-BH4). It was found that 10 members of the family induce apoptosis (for example, Bax, Bcl-xs, Bid, etc.), and 6 make antiapoptotic actions (for example, Bcl-2, Bcl-xl, Mcl-1 etc.), that in case of their increased expression leads to tumor development. Proteins, coded by these proapoptotic genes, cause releasing of CytC, dATP,

apoptosis-inducing factor (Aif) and DNAase into cytosole. CytC together with dATP activate cytoplasmic protein Apaf-1, and apoptosome is formed, in which activation of procaspase 9 into active caspase-9 proceeds. The latter, in turn, activates a killer caspase 3. Aif and DNAases, released from mitochondria, perform additional non-caspase pathway of apoptosis (Brenner et al., 2000). The core of apoptosome is composed of the next proteins: pro-caspase-9, CytC, ADP/ATP, Apaf-1 (Riedl et al., 2007; Fadeel et al., 2008), although some additional proteins such as XIAP, Hsp70 and Aven (Chao et al., 2000), may be involved in the process. Possibly, Bcl-2 is also a constituent of the apoptosome (Brunell et al., 2009; Saelens et al., 2004). Probably, the apoptosome composition may be altered in dependence of the cell type.

It is considered, that activation of Bax by stress-activated protein BH3 of Bcl-2 family is the most often scenario of apoptosis (Portt et al., 2010; Chipuk et al., 2008). Mitochondria also include other proapoptotic factors: Smac/Diablo, serine protease Omi/HtrA2, endonuclease G. This makes mitochondria to be a central unit of the apoptosis regulation.

Changes of redox state of CytC potentially may regulate own way of apoptosis at relatively late stage of the process (*Green, 2005*). Although the CytC release from mitochondria is irreversible the recent data evidence that execution of the last stage of apoptosis is subjected to strict control, even after its releasing (Martin et al., 2005). There are several possible levels for such regulation and redox state of cytosolic CytC may be one of them (Hancock et al., 2001).

After releasing from mitochondria, CytC participates actively in the apoptosome assembling. Cytosolic Apaf-1 exists as inactive monomeric closed conformation till receiving of the apoptotic signal - CytC appearance in the cytosole, which binds with WD40 domains of Apaf-1, stabilizing its open conformation. In such a conformation the latter hydrolyses dATP or ATP, associated with nucleotide-binding domain. This is accompanied by nucleotide exchanges, which cause oligomerization of 7 molecules of Apaf-1 into heptamer, and this provides a possibility to activate procaspase-9 through CARD domains of Apaf-1 and procaspase-9 (Kim et al., 2005).

At least, there are three possible mechanisms due to which the redox state of CytC may influence on apoptosome activation (Qi et al., 1996; Yu et al., 2001; Olteanu et al., 2003). All of them are linked with different Apaf-1 activating ability in conditions of oxidized and reduced forms of CytC (Brown et al., 2008). In particular, different forms of CytC may possess different affinity to ATP, binding to which inhibits activation of Apaf-1 (Chandra et al., 2006). Thus, if the reduced form of CytC has more ability to bind ATP, this may explain its activation inability. The same effect is also may be a result of excessive production of ATP in the organism. There are data that CytC suppresses activation of caspase-9 that favors tumor development, in some tumor cells (Ferguson et al., 2003).

Recent studies demonstrated a multiply function of p53, which may act as tumor suppressor as well as regulator of ageing, autophagy and metabolism (Farnebo et al., 2010; Szeltukhin et al., 2010). Oncogene activation or disregulation of cell cycle leads to activation of p53 as a response to oncogenic stress. Level of p53 is strictly regulated through post-translational modifications such as phosphorylation and acetylation. However, mutations of p53, which is observed in 50% of human tumors, allow tumor cells to escape from p53 response and this leads to tumor progression. Recent studies demonstrate possibilities to regulate p53 at p53 mRNA level (Zhang et al., 2008; Le et al., 2009; Vilborg et al., 2009), that grants a hope to successfully use p53 against cancer.

Thus, the mechanisms of p53 activation after DNA damage remain obscure. In particular, this concerns a role of poly(ADP-ribose)-polymerase (PARP), that is significant in recognition of DNA damages and reparation. A process of poly(ADP-ribosylation) is a conversion of β-NAD^+ into ADP-ribose, which than binds to acceptor proteins and is used for formation of polymers of different length and structure. Correct turnover of PAR is provided by coordinated actions of enzymes PARP and PARG, which are responsible for polymerization and degradation, correspondingly. Hyperactivation of PARP leads to depletion of intracellular NAD+ and inflammatory states. Moreover, biosynthesis of PARP needs large energy expences, that in some cases, due to its hyperexpression (for example, in multiple breaks in DNA), leads to ATP depletion and cell death. In some cases it is suggested to use this property for coordinated attack at tumor cells (Loor et al., 2010), using combination of antitumor preparations and inhibitors of PARP (Giansanti et al., 2010).

PARP also may directly induce apoptosis through PAR production that stimulates mitochondria to release Aif (by caspase-independent mechanism) (Loor et al., 2010). However, it is necessary to take into account that loss of PARP in case of some cell lines is followed by repression of p53 induction, but these differences are not expressed clearly at the other cell models (Yu et al., 2006).

If in the cytoplasm p53 activates mitochondrial apoptotic pathway, then its main role in the nucleus is up-regulation of transcription of RNA-polymerase II, what is linked with such genes as p21, Bax, Puma, Noxa. p53 also may play a role of an inhibitor of transcription of RNA-polymerase I in nucleolus (Fumagalli et al., 2009; Lee et al., 2010), disrupting SL1-UBF interactions (Tuan et al., 1999), that influences on biogenesis of ribosome subunit.

Apoptotic actions of p53 are tightly linked with functions of DNA-polymerases (Pol), part of which are a zinc-dependent ones and may contain 2-4 g of zinc atom per mole of the enzyme (Slater et al., 1971). Moreover, zinc acts through Zn-finger transcription factors, providing identification of DNA sites by proteins and own active influence on oxidative stress products. However, the Zn-fingers may affect apoptosis, not only through p53. In the rare cases of acute promyelocytic leukemia the promyelocytic leukemia zinc finger (PLZF) gene encodes a Krüppel-type zinc finger transcription factor (Parrado et al., 2004), possibly with modified structure of binding sites. Its influence on the differentiation, cancer cell growth and apoptosis is not yet clear, but it is known that proapoptotic Bid is a target of PLZF repression, that leads to dangerous effects of cell resistance to apoptosis.

To control expression in cell division, zinc is essential for phase G2 and induction of DNA-polymerase α (family B). However, part of DNA-Pol-s is not represented by metalenzymes and zinc ions inhibit their polymerase and endonuclease activity (Slaby et al., 1984). DNA-Pol-s signaling needs further thorough studies, because it is linked with oncogenesis very tightly**.** In the last time, a particular interest is directed at DNA-Pol-s of translension synthesis (Y-family), which is an important strategy for cell's survival. After UV-damage DNA, DNA-Pol h (performing perfect synthesis of DNA at damaged template) is accumulated in sites of replication of damaged region through interaction with monoubiquitinated PCNA, and molecular shaperone Hsp90 provides nuclear focusing of DNA-Pol h, in particular, through control of stability, facilitating its folding into active form (Sekimoto et al., 2010). In DNA-Pol ι and Rev1 a structure of ubiquitin-binding motifs was determined (Bomar et al., 2010). Another important aspect is to consider replication regarding switching of DNA-Pol δ (family B) to DNA-Pol η (family Y of translesion synthesis) (Masuda et al., 2010). It was shown that

polymerase reaction of switching is stimulated by mono-ubiquitination of PCNA in dependence on UBD Zn-finger Pol η.

In the second way of apoptosis binding of cell death receptors with ligands activates caspase 8 (or caspase 2), which activates caspase 3 independently. In this case, signal transduction may proceed through proteins FADD/MORT1: N-terminal regions (DED) of these proteins and caspase 8 bind each other with consequent activation of the latter. In case of activation of TNF-R1 an adaptor protein TRADD is used.

After interaction between FasR and FasL the complex of membrane part of the receptor and special proteins (death-inducing signal complex, DISC) is formed. This complex initiates cascade activation of caspases, i.e. activation of caspase-dependent endonucleases takes place. All these processes lead finally to degradation of DNA, to oligonucleosome fragments formation of apoptotic bodies (Filchenkov, 2009).

This apoptotic way interlaces with the previous one, because, for example, it is known, that releasing of CytC from mitochondria may proceed through activation of protein Bid by caspase 8 and its conversion into active form (Brunelle et al., 2009), that may increase receptor-induced apoptosis.

Among proteins-inhibitors of the process of receptor-mediated apoptosis it is necessary to pay attention at FLIP- the inhibitor of caspase 8 (Mates et al., 2001). Proteins IAP-1 and 2, which block activation of caspase 9, inhibit non-receptor apoptosis (Brenner et al., 2000).

Mutations in different apoptosis-controlling genes were determined as causes and/or promoting factors, which may lead to different human diseases (Mullauer et al., 2001). For example, defects in the receptor of transmembrane tumor necrosis factor (TNF-R1) lead to development of fever syndromes. Mutation in Fas is observed in case of malignant lymphomas. Mutation in Fas-L was described in patients with lymphatic nodes damage. Defects of caspase 10 are associated with autoimmune lymph proliferative syndrome type II. Intracellular pro-apoptotic molecule Bcl-10 mutates often in the mucous membrane of lymphoid tissue (MALT) of lymphoma. p53, associated with DNA damages, and proapoptotic molecule Bax, which is able to disrupt an integrity of mitochondrial membranes, also mutate in malignant tumors. Anti-apoptotic proteins – Bcl-2, c-IAP-2 and neuronal apoptosis inhibitor – protein 1 (NAIP 1) are altered in follicular lymphoma, MALT-lymphoma and spinal muscular atrophy, respectively.

Ubiquitin-proteasome way, which is responsible for maintaining of a balance between synthesis of proteins and their degradation, is of great importance for apoptosis as well as many cellular processes, (Burger and Seth, 2005; Orlowski et al., 2003; Landis-Piwowar et al., 2006). Family of ubiquitin-E3-ligases catalyzes the last stage till degradation by proteasomes (Hershko et al., 1998), and dis-regulation of their activity leads to proliferative diseases and cancer (Nalepa et al., 2006). Proteasome is included into pathogenesis of several human diseases (Ciechanover, 1998). 20S proteasome, a proteolytic core of 26S proteasome complex, possesses multiple peptidase activity (including, chymotrypsin-like, trypsin-like etc.). Inhibition of chymotrypsin-like (but not trypsin-like) activity of the proteasome is a strong stimuli inducing apoptosis (An et al., 1998; Lopes et al., 1997). Ability of inhibitors depends on structure and functioning of proteasome and ubiquitin-proteasome complexes, and the last achievements, regarding mechanisms of their action, are described in the work of (Jung et al., 2009).

Due to this, inhibitors of proteasomes, as well as inhibitors of enzymes and regulatory proteins, controlling the cell cycle, are among preparations of “permissive” effect. The latters include cyclin-dependent kinases (for example, flavopyridol), tyrosine kinases (for example, STI-571, Gleevec). Inhibitors of farnesyl transferase also promote apoptosis.

Yeast represents a useful model to study the programmed cell death. They possess not only characteristic markers of apoptotic cell death in expression of inductors of apoptosis or introduction of apoptosis-inducing preparations (for example, hydrogen peroxide), but contain homologs of several components of apoptotic mechanism, identified in mammals, such as caspases, Aif and IAPs. Using the yeast model, apoptosis factors, such as BIR-proteins (IAP-repeats), have been studied in detail (Owsianowski et al., 2008). BIR-containing proteins are characterized by presence of multiple domains, such as BIR, RING, CARD, and UBC. RING domains provide the protein with ubiquitin-ligase activity (Brahemi et al., 2010); UBC addresses to ubiquitin-conjugate domain. Presence of both domains in components of apoptotic mechanism maintains the link between apoptosis and protein degradation.

In the recent time a great attention in apoptosis consideration is given to autophagy (He et al., 2009), especially, to shaperone-dependent process, which proceeds with participation of cytoplasmic proteins - shaperones of Hsp-70 family, complementary proteins and LAMP-2. The latter serves as membrane receptor of a complex of shaperone with a protein subjected to be transported into lysosome. It is considered, that autophagy may be a part of caspase-independent apoptosis (Huang et al., 2007).

A possibility to regulate the apoptosis by pharmacological preparations attracts a great attention today (Zivny et al., 2010). Inductors of apoptosis are practically all preparations, independently on their nature, which damage nucleic acids structure, disrupt the cell cycle, initiate receptor-mediated mechanisms destabilize the mitochondrial membrane. Biotechnological recombinant ligands of apoptogenic receptors (FasL, TNF, TRAIL) and apoptogenic proteins (apoptin, VP3) are used. There are anti-sensor oligodesoxynucleotides against Bcl-2, which are used separately as well as in combination with vectors of proapoptogenes Bax and Bcl-xs, “wild type” vector of proapoptogene p53. There are also synthetic imitators of proapoptotic proteins of Bcl-2 family.

Almost all presented above pathways are zinc-dependent ones, where zinc ions are included as intermediate factor, acting, in dependence on their concentration and presence of additional factors, like inhibitor of apoptosis or strong cytotoxic agent influencing on conformational state of the process participants. Zinc action almost always is mediated process and it proceeds through relatively complicated and different ways. We do not know about them in detail and it is necessary to understand their role. Correct functioning of the zinc ion in the organism means a very fine balance of uptake, storage and transport from cell to extracellular space, participation in cell signalling pathways. Any disruption of the balance leads to some disorder in organs and development of diseases.

Internal and external signals of apoptosis participate in regulation of fate of each cell, and signals of cell growth and death are interlaced greatly and, possibly, they represent different expressions of common mechanism, forming united cycle. Nerve growth factor (NGF) and T-cell receptor (TCR) are examples of this. The first induces either growth or death of neurons; the second induces either differentiation or death of thymocytes. Consequently, the same signal or the receptor can produce multi-directional instructions.

2.2 Concentration-Dependent Influence of Zinc Ions on Apoptosis

Zinc ions like calcium ions participate in cell signalling as secondary messenger (Zalewski et al., 2005; Maret, 2011). They dynamically regulate three important signalling pathways, stimulating tyrosine kinase and phosphatidylinositol-3-kinase/Akt and suppressing protein kinase C (Hajnal, 2002; Korichneva et al., 2002; Wu et al., 2003).

However, a special attention should be given to the fact, that zinc influence is a concentration-dependent process. Although a concentration less than 50 μM is considered as protective and non-toxic (i.e apoptosis inhibiting), during studying of mononuclear cells of peripheric blood (PBMCs) a portion of apoptotic cells were increased slightly in the presence of zinc in concentration of 30 μM (Chang et al., 2006). Large amount of zinc (concentrations up to 100 μM are considered as pharmacological ones) increases effects of different inducers of apoptosis (Schrantz et al., 2001; Wood et al., 2001), and in concentrations more than 100 μM zinc become cytotoxic agent. In some cell lines, in particular, neurons and lymphocytes, necrotic and apoptotic effects are observed in zinc concentrations more than 200 μM (Hamatake et al., 2000). Usage of zinc for anti-apoptotic purposes is suggested to be non-effective to provide long-term survival of cells. Zinc may only block apoptosis without providing of normal cell cycle restoration (Fraker et al., 1997).

Zinc concentrations of 33.7-75 μM are able to induce apoptosis in cancer cells of TS/adenocarcinoma of mouse mammary (Provinciali et al., 2002) through increasing of ROS and p53 level and Fas/FasL mRNA expression. Induction of metallothionein (MT) in these cells after addition of zinc was weak. Treatment of tumor cells by NAC prevented a Zn-induced apoptosis.

In PBMC cells at zinc concentrations of 30-100 μM no significant differences in expression of Bcl-2, Bcl-xl and NF-κB were observed. A noticeable decreasing was observed at concentration ~300 μM, while c-fos expression was increased at concentration ~100 μM. At the same time, zinc stimulated expression of cytokines IL-1β, IL-6, IL-12, and also IFN-γ mRNA and TNF-α at maximum pharmacological concentration 100 μM and even at toxic concentration of 1000 μM (Chang et al., 2006). Beginning from concentration of ~100 μM zinc induces apoptosis linked with increased expression of caspase-3 and proapoptotic genes, including Fas and FasL. Caspase-dependent, i.e. mitochondria-mediated internal way, as well as external (receptor) way and caspase-independent apoptosis play a role in the process of PBMC-cells apoptosis. Cases of direct effects of zinc at mitochondria were also observed (Feng et al., 2002; Undergasser et al., 2000). Recent studies of genome stability in the presence of two Zn-containing compounds: sulfate and carnosine (ZnC) demonstrated *in vitro* (Sharif et al., 2011) that their optimum concentration, providing lack of damages in DNA and cytotoxicity for lymphoblast cell line, is 4-16 μM.

It is known (Seve et al., 2002), that decreasing of intracellular concentration of zinc may induce characteristic apoptosis with formation of apoptotic bodies and condensation and fragmentation of nuclear DNA. Zinc deficiency activates caspases -3, -8, -9, which are responsible for proteolysis of several protein targets, such as PARP, and transcription factors. In this case (in Zn-deficiency) increase of a number of apoptotic cells in different animal tissues was observed, including in cells of intestinal epithelium, skin, thymus gland, testis, retina and pancreas (Truang-Tran et al., 2001). Comparison of hystopathological alterations in thymus, testis, skin, gullet, liver and kidney and their relationships with apoptosis in absence of zinc in ration and standard Zn-diet were performed on rats (Nodera et al., 2001). Significant morphological changes were observed in tissues of rats lacking of

zinc in the food. However, atrophy in different extent and in different time of Zn-deficiency was observed in all studied samples. Thymus and testis were more sensitive to zinc absence. Observed pathologies and apoptosis depend on zinc concentration in tissues (i.e., labile zinc), and in thymocytes both zinc effects (inhibiting and inducing) on apoptosis influence G0/G1 phases (Provinciali et al., 1995).

Addition of 30 μM of zinc *in vitro* is able to inhibit readily spontaneous as well as induced by ethanol apoptosis of PBMC (among of them CD4+T-helper cells) cells, isolated from the blood of healthy donors and patients with liver cirrosis, in which initially addition of ethanol caused apoptotic events (Szuster-Ciesielska et al., 2005). It is considered that in this case zinc prevented the mitochondrial way of cell death. Addition of zinc inhibits apoptosis of liver cells induced by alcohol (Kang et al., 2005), in this its action in the liver and out of the organ is distinguished. Decreasing the zinc depletion in the liver induced by ethanol and suppressing increased activity of cytochrome P-450, zinc simultaneously increases activity of alcohol dehydrogenase (probably, through suppression of oxidative stress). In the same time, zinc increases antioxidant activity in the liver linked with glutathione and suppresses Fas/FasL-mediated way of apoptosis and prevents endotoxemy, which causes inhibition of TNF-α production in the liver. Influence of zinc in and outside the liver is independent of MT.

During the apoptosis, zinc in concentration of 1-6 мМ inhibits enzymatic activity of Ca^{2+}- and Mg^{2+}-dependent endonucleases, including acidic endonucleases, such as DNAase II. Zinc deficiency alters lipid composition, enzyme activity and protein composition of the cell membrane and linked cytoskeleton, thereby increasing permeability of membranes (Henning et al., 1999).

Additional dietary, containing zinc, may prevent effects of other inducers of apoptosis, which in some cases lead to Zn-deficiency. Thus, hystopathological action of fluoran is in increasing of apoptosis through fluor-induced depletion of zinc in testicles of rodent embryos. Introduction of additional Zn-containing ration allows to protect seminiferous tubules (Krasowska et al., 2004) by decrease of fluorine toxicity.

In a work (Kozlowski et al., 2009) the influence of zinc on apoptosis of neurons is represented as cyclic mechanism. Accounting a significant role of zinc in oxidative stress and mitochondrial disfunction, firstly ROS induce zinc releasing from MT-proteins, then zinc uptake leads to mitochondrial disfunction and increased mitochondrial generation of ROS. This, in turn, promotes futher mobilization of zinc out of MT and its elevation in a cytosole, in the result zinc activates mitochondrial consumption of zinc and apoptosis. In chronic diseases this cycle is strenghened and fixed by increasing of DNA-mutations (which also are linked with oxidative stress induced by zinc) and expresion of defect proteins, that makes mitochindria less active in their fighting with ROS.

Tumor suppressor p53 is a transcription factor, which contains a single zinc ion near DNA-binding site. Zinc is necessary for specific DNA binding as well as for activation of transcription. This is explained by dominating role of zinc in correct folding of p53. Zinc deficiency as well as zinc excess leads to misfolfing and loss of protein functions. Zinc-binding status of p53 in a cell is directly associated with presence of oncogenic mutations and, in case of metal binding disruption or its loss, this leads to uncontrolled cell growth and cancer. This effect may be annuled by metal-containing shaperones (Loh, 2010).

Most tumors occur in case of p53 mutations (mainly, missence mutations), because p53, being in normal structure state, activates transcription of genes involved in cell cycle

suppression, DNA-reparation, apoptosis and ageing in responce to DNA damages, degradation of telomeres or other oncogenic stress signals. Moreover, p53 may promote apoptosis through transcription-independent mechanism mediated by mitochondria (Green et al., 2009). Structural pecuiliarities and mechanism of p53 folding are considered in detail in (Loh, 2010).

All this makes zinc as a possible agent for cancer treatment. For example, zinc ions influence susceptibility to induction of malignant lymphoid cells (Filchenkov et al., 2001). At concentration of 150 mM or higher zinc induced necrosis and apoptosis in thyroid cancer cell lines. Necrosis was dose-dependent (on the concentration of zinc) process, while apoptosis did not grow up with increasing of zinc concentration. The expression of anti-apoptotic Bad was markedly increased, whereas expression of proapoptotic proteins Bax and Bad decreased. Zinc induced the rapid degradation of IκB, and an increase in nuclear transcription factor NF-κB. These observations indicate that the antiapoptotic pathways were activated in thyroid cancer cells by zinc, and this may be a mechanism for self-protection against apoptosis, that may be the basis of resistance of cancer cells to apoptosis (Iitaka et al., 2001).

Dose-dependent anti-proliferative action of zinc was studied on cell lines of pancreatic adenocarcinoma and normal primary fibroblasts by increasing a dose of zinc ions (Donadelli et al., 2009). Increasing inhibition was observed in all cell lines, but is less noticeable in fibroblasts. Addition of ionophore - PDTC increases zinc absorption in all cells almost by factor 12 and combined action of Zn and PDTC inhibits proliferation of cancer cells more effectively than even hemecytabine, the gold standard of chemotherapeutic agents for pancreas cancer. At this neither caspase 3 nor caspase 8 were not activated after administration of Zn/PDTC (and common inhibitor of caspases Z-VAD-FMK was ineffective to stop Zn/PDTC-induced cell death). It is suggested that there is a splash of ROS that is responsible for translocation of Aif with subsequent fragmentation of DNA that also is not linked with CytC releasing. Thus, in this case, namely, ROS-generation is the factor, that induces strong apoptosis of cancer cells. However, normal primary fibroblasts were more resistant to action of Zn/PDTC, that is explained by inhibition of p53 expression after treatment of cells by Zn/PDTC. This decreases contribution of direct action of p53 on apoptosis and partly protects cells from cytotoxic action of the preparation as seen in Figure 1.

Inhibitors of proteasomes are therapeutic agents in cancer treatment. In breast cancer BCA-2 plays significant role and this protein is a member of ubiquitin-E3-ligase family represents RING-Zn-finger protein and contains a double zinc-binding motif. Enzymatic activity of the protein is lost completely after point mutation of key zinc-binding cysteine residue (Burger, Gao et al., 2005; Amemiya et al., 2008). So, for treatment it is recommended to perform screening of compounds with ability to extract zinc ion from BCA-2 (Brahemi et al., 2010), and due to this to possess anti-tumor activity. In particular, zinc-extracting aldehyde dehydrogenase is such a compound.

Disruption of zinc homeostasis in old age is of particular risc that provokes some diseases. Detailed consideration of apoptosis in ageing is in the next review (Zhang et al., 2002).

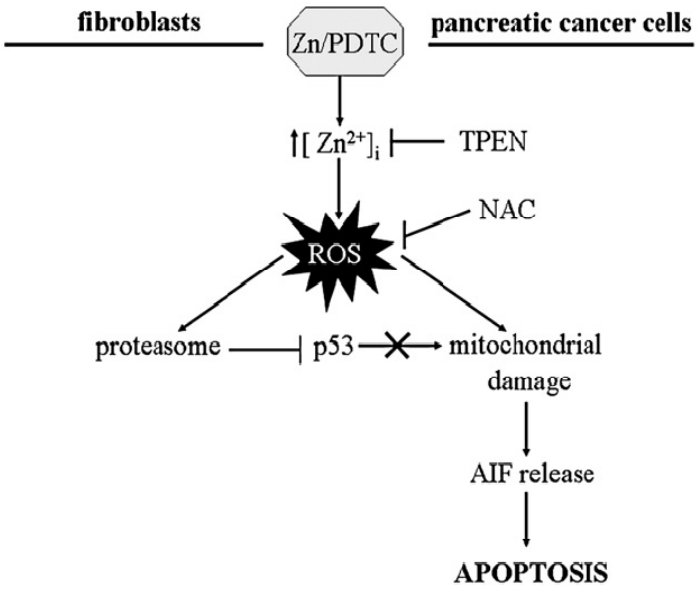

Fig. 1. Model of action of Zn/PDTC
(Source: Donadelli et al., 2009)

Zinc is able to influence expression of PKC-family through Fas-receptor. For example, nPKCδ and θ may be subjected to limited proteolysis in apoptosis nPKCε is specifically cleaved and generates C-terminal fragments of 43 kDa and 36-kDa during apoptosis, induced by chemotherapeutic preparations (Koriyama et al., 1999). However, the cleavage is completely inhibited by pre-treatment with caspase-3 inhibitor. Moreover, nPKCε was cleaved by purififed recombinant caspase-3 in lysates of untreated U937 cells with generation of 43 kDa fragment, which was indentical by size to the fragment observed *in vivo*. Thus, participation of PKC in apoptosis is regulated differently in dependence of various inductors of apoptosis.

Recent studies particularly concern signaling pathways which make effects on proliferation and apoptosis of cells through mitogen-activated protein kinases (MAPKs) (Kim et al., 2010), including: extracellular kinase ERK, p38 and C-Jun-N-kinase (JNK). MAPK-signaling pathways are activated by extra- and intracellular inductors, including peptide growth factors, cytokines, hormones and cellular stresses: oxidative and ER, and deviations from strict controlling of these ways (in particular, by zinc as antioxidant component of the system) lead to different diseases. It is known, that permanent activation of JNK or p38 signaling pathways mediates apoptosis of neurons in AD, PD, and ALS, while ERK plays key role in some stages of tumors genesis. Activation of MAP-kinase cascade takes place in response to specific stresses (Silva et al., 2005).

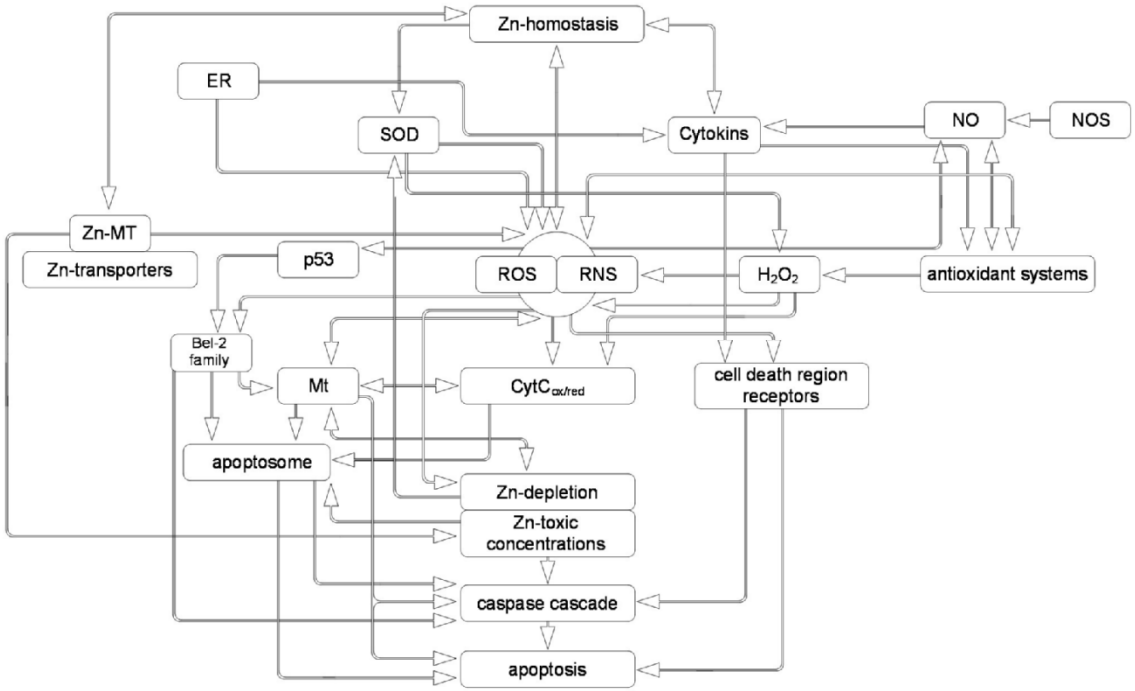

Fig. 2. Antioxidant cycle of zinc

Studies of vesicants effects using CEES in concentration of 100-1000 μM as an example, on expression of antioxidants and eicosanoids (Black et al., 2010) showed significant increasing of oxidative stress markers level in combination with increasing of expression of SOD, CAT and glutathione-S-transferase. Simultaneously, activation of JNK and p38 MAP-kinase took place, signaling pathways of which regulate expression of antioxidants, and also of prostaglandins and leucotriene synthase. Thus, modulation of expression of antioxidants and enzymes producing inflammatory mediators is observed, i.e. adaptive process is switched on to limit damages of tissues by vesicants, which induce the oxidative stress. So, zinc is included in adaptive processes control.

In Fig. 2 and 3 interrelationships of zinc and main participants of apoptosis are represented. This is, of course, not a full picture. It is suggested that zinc is included in numerous cycles of ways (and, seemingly, closed) leading to apoptosis. The smallest and most studied is the antioxidant cycle. However, due to more complete studying, the cycles become more wide and diverse, are interlaced with each other and include more wide inter-relationships.

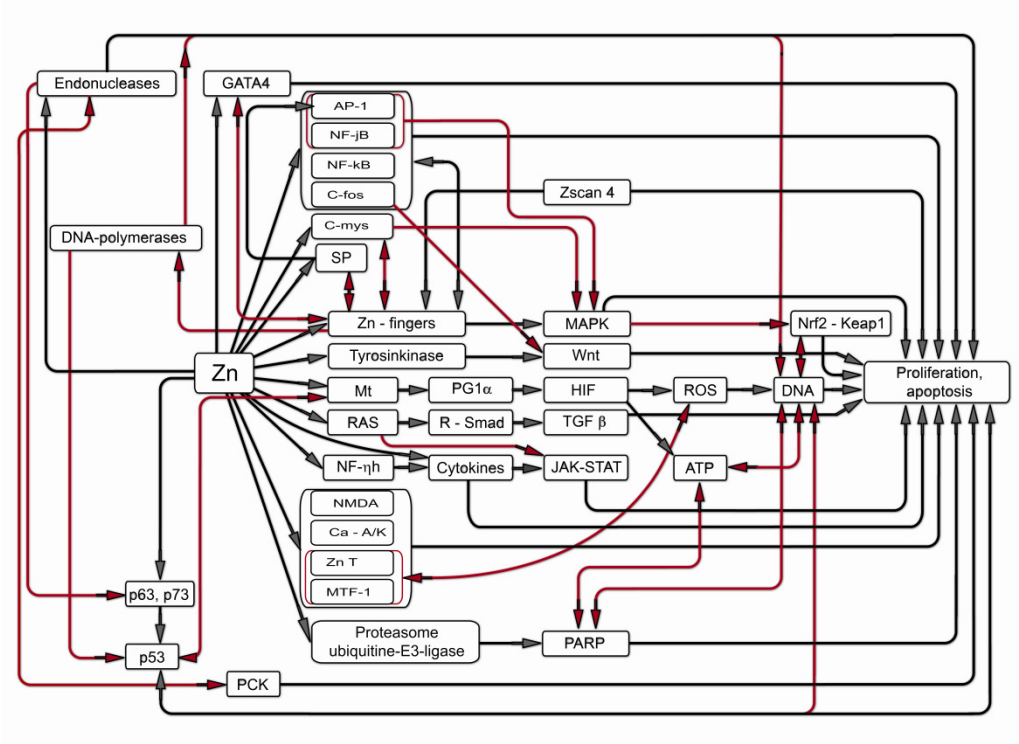

Fig. 3. Relationship zinc to some signaling rathways and transcription factors

3. UPTAKE, STORAGE AND TRANSPORT OF ZINC IN THE ORGANISM

3.1 Metallothioneins

The most important active absorbers, keepers and manipulators of zinc in the body are metallothioneins (MT), which represent cystein-containing low molecular weight intracellular proteins. They are induced in cells and tissues by transcription factor-1 (MTF-1) in the presence of metal ions (as a response to their appearance), which they bind (Gromova et

al., 2005; Minami et al., 2009). Moreover, MT are induced in response to stress (in some cases a responsive hyperexpression is possible) (Lim et al., 2010) by way of endogenic or exogenic inductors including glucocorticoids, proinflammatory cytokines, oxidants, electrophylic compounds and xenobiotics (Palmiter, 1998). Expression of MT demonstrates direct relationship with IL-6 level and reverse with IL-2 (Gromova et al., 2005). MT-proteins demonstrate high affinity to zinc (K_{Zn} = 3.2 10^{13} M^{-1} at pH 7.4) and bind seven zinc ions due to peculiarities of metal coordination with cysteine ligands (Mocchegiani et al., 2005; Jacob et al., 1998). Recently, development of ESI-MS method gives possibilities to obtain more complete information regarding mechanism of zinc binding to MT and its releasing (Lesycszyn and Blindauer, 2010). So, a structural chemistry of these proteins is under active development to determine the mechanism of cluster formation of different isoforms of MT with metals and prediction of their structure and, correspondingly, properties for metal-traffick (Blindauer et al., 2010). There are two main types of clusters in MT, and both form tetraedric coordination sphere. One unit (β-type) – M_3Cys_9 – contains three atoms of the metal and three sulfide bridges which form six member ring. Each of the other 6 thiolates coordinates one atom of the metal and each atom of the metal binds two these terminal Cys-residues. Such rings were discovered in mammalian MTs. A cluster M_4Cys_{11} (α-type) with two six member rings was found in another domain of MT. However, also other possibilities for binding are under discussion as well as a question why, namely, by such a way the metal binding and trafficking proceed and what determine specificity of MTs to the metals. Possibly (Waldron et al., 2009) that transcription, availability and allosteric properties of a protein which is expressed in response to appearance of metal ions (that, in turn, depends on the type of binding and/or determines it) mutually combine metal trafficking and metallospecificty. There are evidences (*in vitro*) regarding isoform-specific partnership of zinc and cadmium in two isoforms of MT from *C. Elegans* (Leszczyszyn et al., 2011). Considering clusters of MT with Zn and Cd, using DFT, thermodynamic stability of heteroclusters has been demonstrated (Jensen et al., 2010). It is known (Kothinti et al., 2009) that Cd can compete with Zn for metal-binding sites leading to structural changes, misfolging and loss of enzyme activity. The increase in Cd-toxicity is particularly noticeable in condition of Zn-deficiency (Weihong et al., 2009) that is expressed in damages of signaling pathways (Thevenod, 2009) and of gene regulation (Tabatabai et al., 2005).

However, the question how cells direct regular metals to regular proteins (isoforms), is still opened, especially, that concerns the very similar and by affinity and by close joint co-existence of zinc and cadmium. It is supposed that there is discrimination between zinc, necessary for an organism, and toxic cadmium, based on the difference in affinity to some sites in MT. In particular, in plants such a difference is observed in existence of isolated only zinc-binding sites (Leszczyszyn, White et al., 2010).

Because a key property of metalloproteins and metal-enzymes is an affinity of a metal M ion to protein ligand P which is determined by dissociation constant K_D = [M][P]/[MP], then its precise determination is of significance for quantitative understanding of a metal selection by proteins and its specialization (Xiao et al., 2010). Kinetic lability of a metal depends on thiolate surrounding of the metal, so MT may readily exchange by metal ions with other proteins. Besides Zn_7T (direct MT) Zn_6T, Zn_5T and also Zn_4T exist, and their formation depends on protein concentration and availability (presence) of zinc ion (Maret et al., 2010). In this it is necessary to account that MT exist in oxidized, polymerized, thiol-modified and other altered forms (Krezel and Maret, 2007), and this influences binding and releasing of zinc.

At the present time, there are known 4 classes of MT in humans, including 17 isoforms (Lim et al., 2010). More distributed MT-1, MT-2 were well described, and MT-3 and MT-4 are less studied (Coyle et al., 2002), which are presented in uriniferous tubules, neurons, prostate tissues and in epithelium of skin and tongue, correspondingly (Garrett et al.,. 1999; Garrett, Sens, Somji et al., 1999). MT have a molecular weight up to 6-7 kDa and they are able to bind a wide range of metals (Zn, Cd, Cu, Ag, Au, Bi, Hg, Pb) (Gromova et al., 2005). Metals induce expression of these proteins in different tissues (brain, liver, myocardium, etc.). Zinc deficiency may induce synthesis of metallothionein, which is able not only to bind redox-active metals, but also to capture hydroxyl radicals due to its cysteine residues (Patricia et al., 2000).

Besides metals, MT are induced by steroids in rats, carcinogenes in mice, chemical compounds causing oxidative stress in rodents, ionizing and UV radiation. Induction of MT-1 does not proceed in the presence of EDTA, in absence of zinc ions in culture medium and also in case of disruption of zinc transport into a cell.

Besides the function to prevent distribution of ROS, and also active forms of nitrogen (RNS), MT-1 and MT-2 perform transport of zinc ions and maintain concentration of intracellular free zinc (Feng et al., 2002; Krezel and Maret, 2007).

For homeostasis of neuronal zinc MT-3 is more significant in critical regions of the brain such as hippocampus, where it is presented abundantly in glutamateergic endings, significantly enriched by vesicular zinc (*Kozlowski et al., 2009*). It is considered that phenol-contaning antioxidants activate transcription of MT-1 due to Zn-dependent mechanism, in which binding of transcription factor MTF-1, activated by metals, with structures of promotor of gene MT-1, which are regulated by the metal (Gromova et al., 2005). From one side, induction of MT protects tissues and the brain from heavy metals effects and in the MT absence their sensitivity to action of oxidative stress factors is increased. In the same time, the oxidative stress, interfering binding of zinc with MT, acts as key regulator of Zn-homeostasis (Kozlowski et al., 2009).

In the present time a great attention is given to MT-proteins expression and, correspondingly, to zinc homeostasis in old organisms (Maret, 2008). Some studies indicate growth of MT-1 and MT-2 genes expression in astrocytes of old rats (Mocchegiani et al., 2001) and MT-3 expression of genes in old hippocampus (Giacconi et al., 2003). The role of MT is described in detail in a review (Swindell, 2011).

Kainate-induced excitotoxicity leads to MT-1 hyperexpression that causes delay of neuronal degeneration and death of cells (Penkowa et al., 2005). This is, seemingly, linked with anti-inflammatory and antioxidant activity of MT-1 and, in part, with direct MT-1- mediated stimulation of IL-10, growth factor and neurotrophines. Because MT-proteins represent protection factor against stress conditions, than their abnormal expression in the old brain may reflect endogenic response to permanent oxidative stress. On the other side, if all the isoforms are increased due to permanent high level of inflammatory cytokines (IL-1 and IL-6), then protective effect of MT may be lost due to de-regulation of zinc homeostasis (Mocchegiani et al., 2001). In the old brain, permanent and maintained high levels of IL-1 and IL-6, provoke continiuos expression of MT gene, maintaining presence of limited zinc releasing in responce to intracellular signal (Croix et al., 2002). In connection with increasing of pro-inflammatory cytokines IL-1, IL-6 and TNF-α levels in the blood serum in old age a situation is arisen when permanent age inflammatory states in ageing may be defined as “inflammatory ageing” (Franceschi et al., 2000) with high expression of MT- proteins in

astrocytes and neurons of hippocampus as defence measures against long influence of inflammatory agents.

ROS may be generated by extra-mitochondrial ways, which include increasing of activity of NADPH-oxidase and induction of neuronal nNOS, which produces peroxynitrite (ONOO-) jointly with superoxide. MT interacts with NO, amount of which as amount of ROS are increased during oxidative stress. In biological systems this promotes zinc release through S-nitrosylation (Spahl et al., 2003; Maret, 2011). Then a cyclic mechanism becomes possible, when zinc initiates ROS generation, cellular oxidation promotes further releasing of zinc. Ability to release zinc in connection with changes in cell redox-state provides MT-proteins with reservoir of freely available zinc in oxidative stress conditions (Frederickson et al., 2002). Thus, MT is a key factor which determines the zinc homeostasis.

MT increasing in connection with zinc excess or deficiency was revealed in many diseases. It is considered that MT-proteins have a possibility to protect cells and tissues in case of diabetes mellitus due to their anti-apoptotic and antioxidant effects *in vitro* and *in vivo* (Danielson et al., 1982). Human MT gene was cloned and fused with transduction proteins domains (PTDs) to receive PTD-MT fusion proteins with the aim to overcome shortages of ineffective cellular uptake of MT-protein and its effective intracellular tranportation (Lim et al., 2010). Zinc ions were added to optimize expression, which maintained stability and functional state of fusion proteins like intracellular stable conformation of MT as Zn-MT cluster, which has greater stability than MT *in vitro***.** Fusion proteins PTD-MT protected Ins-1 beta-cells from oxidative stress and apoptosis, induced by gluco-lipotoxicity in conditions of hypoxia or without it and also protected cardiomyocytes from ROS and apoptosis induced in hyperglycemia due to anti-apoptotic activity caused, in particular, by caspase-3 activity decreasing.

Increasing of sensitivity of the liver to damages, caused by alcohol, is linked with zinc and MT decreasing in the liver due to alcohol induced liver disease (Kang et al., 2005).

One of the main properties of MT is binding and dosage of zinc to regulate its availability for zinc-binding enzymes pool (Palmiter, 1998), in particular, zinc fingers, and other factors in order to modulate their DNA-binding efficiency, and expression of several genes, which participate in intracellular antioxidant response (Mocchegiani et al., 2001). Zinc may be also delivered to pro-apoptotic enzymes such as NOS and endonucleases (Mocchegiani et al., 2005), to inhibit their activity and also to PARP-1. Moreover, MT may be involved in direct zinc transfer to transporters, which are linked with inner mitochondrial membrane.

3.2 Zinc Fingers

Significant potential of fixed zinc is contained in proteins named as «zinc fingers". This is a group of transcription factors, including proteins KROX-24 (Zif/268), KROX-20, EGR-3, NGFI-B, NGFI-C, NURR etc. Out of 2000 human genes responsible for transcription factors 900 genes code proteins with Zn-fingers. "Zinc-fingers" domains were revealed in many transcription factors, which provide RNA functioning (Laity et al., 2001). Because point mutation in Kruppel-protein gene, resulting in substitution of only one Cys residue to Ser, that make it impossible to bind zinc ions, is phenotypically developed as deletion of whole gene of the factor, then a conclusion has been made that ability to bind zinc ions is a critical point developing of DNA-binding activity of such factors.

Initiated by zinc deficiency oxidative stress may influence on cell signaling through: transcription factors, containing “Zn fingers” motifs and other sensitive to oxidants transcription factors (for example, NF-jB and AP-1).

DNA-binding domain (motif) of «Zn-fingers» transcription factors coordinate through cysteine folding of structural domains, which participate in intermolecular interactions. Oxidative stress disrupts DNA-binding activity of «Zn-fingers», by mode of oxidation of cysteine residues and, subsequently, due to protein secondary structure alteration (Oteiza et al., 2005). NO may also reversibly inhibit DNA-binding activity of transcription factors, which contain, at least, one cysteine residue (Kroncke et al., 2001).

Activation of AP-1 is mediated by MAPKs: JNK, p38 and ERK. In nervous cells zinc deficiency causes activation of MAPKs: JNK and p38, that leads to high nuclear AP-1-DNA-binding activity and increasing of AP-1-dependent gene expression (Mackenzie et al., 2002). Mainly, H_2O_2 serves as a signal. On the contrary, zinc deficiency leaded to decreasing of MAPK activation: ERK1/2, that did not depend on elevation of H_2O_2, but was linked with decreasing of cell proliferation. It is known that in case of zinc deficiency NF-jB- DNA-binding activity in nuclear extracts from rat testicles, in fibroblasts, glioma cells, T-lymphoblastoid cell line (Oteiza et al., 2005), and human nerublastoma cells (Mackenzie et al., 2004) was decreased.

Similar “Zn-fingers”-domains were revealed in polypeptide chains of receptors of thyroid or steroid hormons, which, after their translocation into the nucleus, specifically interact with certain DNA sequences, altering levels of transcription of corresponding target genes.

Some of «Zn-fingers» proteins take part in bone and cartilage development (Gans et al., 2004). Some members of this family act as transcription repressors (Tanaka et al., 2002). Sp family of Zn-transcription factors is involved in the development of skeleton, and adequate zinc concentrations may prevent a bone growth delay, which is observed in Zn-deficiency. Thus, zinc deficiency is additionally defined as a risk factor for osteoporosis (Nakashima et al., 2002). Zinc (in the zinc fingers composition) may have decisive significance for normal heart development because its deficiency damages a transcription factor GATA-4 of Zn-fingers and expression of critical genes, which participate in an early stage of heart development (Duffy et al., 2004).

Recently is was established (Zalzman et al., 2010), that gene Zscan4 plays a key role in the ability of murine embryonic stem cells to self-renewal and its protein product – zinc finger protein 494 – is related to a group of «Zn-fingers» proteins. This self-renewal or rejuvenation is concluded in restoration of telomeres length with help of a mechanism of recombination, when more short telomeres interacts with more long ones that promotes increasing of their length. Then gene Zscan4 is inactivated. This gene is not activated in each cell division and only about 5% of embryonic cells express it in a definite time.

Zinc fingers gene products, which interact with retinoblastoma and possess oncogenic properties, were studied (Rossi et al., 2004) in a MCF-7-derivative cell line, expressing protein, which contains zinc finger domain - (MCF-7/znf). Zn-finger domain contained three of eight supposed motifs of Zn-fingers. MCF-7/znf cells demostrated more high growth rates that their parents or control cell lines in the absence of hormones as well as under action of estrogen stimulation. Moreover, they were less sensitive to growth of inhibition by anti-estrogens and showed more high level of expression of cyclins D1 and A. Thus, Zn-fingers domain may be provided with oncogenic activity of RIZ2 gene product.

In the last studies (Decaria et al., 2010) derivatives of Zn-finger-containig proteins and Zn-hydrolases were used to compare their alterations in organisms of different complexity during evolution and establishment of correlation with changes in the environment. It was found that level of Zn-fingers proteins is increased in the course with evolutionary complication.

3.3 Zinc Transporters

Zinc uptaked by a body is distributed between fixed and labile phases. High cellular concentrations of zinc are toxic and accumulation of free zinc ions must be avoided and this is reached through their pumping out of the cell into reserve vesicles, depot-zincosomes**)** or by binding with MT. In case of high level of intracellular zinc and when it is necessary to transfer it, the outflow of zinc through plasmatic membranes may proceed with help of specific Zn-transporter (Formigari et al., 2007) or by binding to intermediate specific proteins (Maret, 2009). In the recent time, there is trend to consider the zinc transport, which proceeds with specific binding of zinc ions with transporters, from thermodynamic and also kinetic positions, because many moments of occurrence of toxic zinc concentrations and, on the contrary, its deficiency in cells are mysterious (Blindauer, Schmid et al., 2010). It is considered, that phenomenon of zinc transport is rather under kinetic than thermodynamic control (Outten et al., 2001). However, sufficient complications and disagreement in defining of thermodynamic as well kinetic parameters are still existed. In the last decade there is a great knowledge expansion in the field of metal ions transport in different biological systems, but mechanisms of intracellular zinc trafficking have not been in full understood yet. Obviously, because affinity of a metal ion to a protein can not be a single factor of transport, then the thermodynamic gradient would be a main criterion. However, a cell manipulates the zinc ions availability by their isolation and limitation of their presence, determining the place and the time of meeting of the metal and a protein (Maret, 2011). The metal ions are transfered from protein to another that requires an intermediate binding in a definite coordination environment. At this stage the conformational states and changes in proteins should determine kinetics of association and dissociation of a metal.

Zinc transport in the organism is performed by groups of so-called carriers or transporters of zinc. One of these groups is hZIP family. In human genome there are 14 ZIP-genes which are grouped into several subsets. They have 8 transmembrane domains and also histidine-rich Zn-binding cytoplasmic region, and amphiphylic part, which is able to form a channel wall for zinc ion (Kabe et al., 2004). It is known (Franklin et al., 2003) that function of hZIP1 and hZIP2 – import of zinc through plasmatic membrane. hZIP4 is in the apical membrane of enterocytes and its expression is activated in Zn-deficiency, and its mutations are responsible for entheropathy acrodermit (Wang et al., 2002), which is characterized by disruption of intestinal absorption of zinc and severe zinc deficiency. Expression of hZIP6 (LIV1) is regulated by estrogen and is increased in breast cancer (Taylor et al., 2003). It is important that Zip2 mRNA level is influenced by intra- and extra-cellular Zn-concentrations, and overexpression of Zip2 resulted in increased Nrf2 activity, higher GCL expression, and increased glutathione synthesis (Rezaei et al., 2008).

Specificity of transporters to bind only with zinc is under discussion today. For example, a zinc transporter ZIP14 is able to transport ferric ions and ZIP8 binds also Mn and Cd (Maret et al., 2010). In this, presence of chelating or redox agents alters kinetics as well as thermodynamics of metal binding. But, possibly, effects of these factors are expanded on the binding specificity through changes in energy landscape of protein molecules (Krupyansky et

al., 2002), and, subsequently, and in their conformational state, if it is considered as a set of permitted conformational states (Orlova et al., 2009).

A family of mediators of cation diffusion is in another group of zinc transporters: ZnT (SLC30A), which includes 10 members in mammals. Most of them have 6 transmembrane domains, N and C-termini of which are at cytoplasm side of the membrane. They have conserved histidine-rich domain between transmembrane segments IV and V, which binds zinc, and also amphiphylic transmembrane segments, which may form a channel for zinc ion (Kabe et al., 2004). ZnT1 predominantly performs regulation of zinc export, in particular, to plasma at base-lateral surface of enterocytes in the duodenum and jejunum. ZnT2 and ZnT4 sequesters zinc in cytoplasmic vesicles, ZnT3 performs specific function, mainly, in a brain and sequesters zinc in pre-synaptic glutamate-containing secretion granules under influence of potential-dependent chloride channel ClC-3 (Lushnikov et al., 2001; Zalewski et al., 2005). ZnT5 is localized in membranes of secretion granule of insulin, pancreas cell enriched in zinc. ZnT6 and ZnT7 are concentrated in Golgi apparatus (Huang et al., 2002), ZnT8 – in endocrine pancreas, and ZnT10 – in the liver and brain (Zalewski et al., 2005).

Mutation in ZnT4 gene is a basis of a syndrome of “death murine milk”, which is caused by nonsense-mutation, leading to defect secretion of zinc to milk (Huang et al., 1997).

At Hep-2 cells it was demonstrated that they contain abundant labile depots of zinc (Rudolf et al., 2005), which may be exhausted by a zinc chelator - TPEN or increased by attraction of external zinc. Changes of intracellular zinc level are sufficient to modify cells sensitivity to apoptosis and provoke pathophysiological changes in the human body due to zinc participation in cell cycle control (Hakue et al., 2003). A special attention is given to studies on zinc transport in the brain (see Chapter 5).

Besides specific zinc transporters, it seems that some Zn-containing proteins may periodically perform the transport function. In particular, the level Zn-protein A2M, which is an inhibitor of proteinases, is linked with blood stream alteration. It is considered (Ivanova, 2008) that the protein may be a zinc-transporting protein in children, and absence of a link between zinc level and A2M in adults is one of the causes of hypertension and ishemic heart disease. In the blood plasma, where about 1% of total zinc in the body is localized, 80% is bound to albumin, which is also served as zinc transporter in the body (Blindauer et al., 2009). It is not excluded, that ACE in some cases may also fulfill Zn-transport functions.

Mitochondria possess high ability to zinc absorption and blockage of this process determines a significant increasing of zinc concentration in a cytosole. Moreover, mitochondria themselves may provide an intracellular reserve, necessary for active mobilization of zinc in case of necessity.

3.4 Angiotensin-Converting Enzyme

It is known that ACE is a dipeptidylcarboxypeptidase and have two active centers. The protein consists of two domains (N- and C-) and contains two atoms of zinc necessary for enzymatic activity development (~10^{-6}M). It cleaves angiotensin I and bradykinin, altering their biological activity, that leads to blood pressure elevation (Corvol et al., 2004). ACE is a key enzyme of the blood pressure regulation and some its inhibitors (captopril, lysinopril etc.) for a long time and firmly were introduced into the practice of hypertension treatment, which sometimes is considered as derivative of excess of permissible limits of inflammation processes. Two isoforms of the enzyme were sufficiently well-studied: full size (150-180

кDa) somatic form (in endothelial, epithelial and neuroepithelial cells) and testicular (~90 кDa) enzyme, representing C-domain and playing a significant role in fertilization and differentiation of cells. However, functions of the enzyme are not limited by this. One of ACE substrate is N-acetyl-Ser-Asp-Lys-Pro (AcSDKP), to which both domains of the enzyme demonstrate activity, but activity of N-domain in 50 times higher than those of C-domain (Rousseau et al., 1995). AcSDKP itself is known as a natural inhibitor of proliferation of hemopoethic stem cells, but it was able, in dependence on concentration, to stimulate proliferation of endothelium cells (Wang et al., 2004), inhibit differentiation of stem cells of bone marrow, activation and migration of macrophages and releasing of pro-inflammatory cytokine TNF-α. Moreover, AcSDKP hampers TGF-β-signalling through suppression of activation of R-Smad with help of nuclear export of Smad-7 (Kanasaki et al., 2003). This makes it as anti-inflammatory and antifibrosis agent in the mechanism of hypertension development (Sharma et al., 2008) and an important participant of apoptosis regulation, because renin-angiotensin system (RAS) in the bone marrow is linked with distribution and differentiation of cells (Haznedaroglu et al., 2003). Renin, ACE, angiotensin II, receptors of angiotensin of 1 and 2 types (AT1 and AT2) (Rodgers et al., 2000; Strawn et al., 2004), and AcSDKP (acting as down-regulating hemopoethic agent (Abai et al., 2002) are the components of RAS. Angiotensin II interacts with AT1-receptor to stimulate differentiation and increase proliferation of predecessors of hemopoetic cells; and this stimulating activity may be blocked, for example, by losartan (Rodgers et al., 2000). Stimulation of AT1/AT2 receptors expresses stimulating/inhibiting action on JAK-STAT signaling pathways, relating to physiological mechanisms of cytokines (Haznedaroglu et al., 2000), which modulate expression of transcription factor c-myc (Xie et al., 2002). C-myc is a nuclear protein of a family of helix-loop-helix/leucine zipper, and acts as transcription factor, included in the regulation of cell proliferation, differentiation and apoptosis (Sheiness et al., 1979).

ACE positively influences hemoblastosis of bone marrow (Aksu et al., 2006), which in acute myeloid leukemia is linked to renin hyperexpression (De la Iglesia et al., 2006).

Effects of ACE inhibitors (captopril, trandolpril) and losartan in concentrations of >1мМ, >0.05 мМ и 0.2 мМ were studied (De la Iglesia et al., 2009), correspondingly, at K562 and K562-transfected with c-myc, Bcl-x and Bcl-2 cell lines. Inhibitors of ACE restrained cell growth, decreased c-myc expression, increasing apoptosis. It is supposed that these effects are linked with angiotensin II-induced activation of Smad-s proteins.

GPI-ase (GPI-anchor protein releasing) activity of ACE (Kondoh et al., 2005, 2008) was revealed, which has particular significance for the testicular form. All this make ACE the enzyme, actively influencing on processes of proliferation and apoptosis, although definite pro- and/or anti-apoptotic functions of ACE require further investigation.

4. ANTIOXIDANT PROPERTIES OF ZINC

Stress, inducing throw of ROS, is the main pro-apoptotic factor, which influences many stages of apoptosis (Figure 2). It is suggested that ROS appearance may serve as a direct activator of Bax through activation of BH3 Bcl-2 Bnip3 protein (Kubli et al., 2008). However, in the same time, stress, as a whole, and specific stresses, in particular, may be a strongest adaptive factor leading to hyper-expression of anti-apoptotic genes (acceptors of ROS, heat shock proteins etc.) and prevention the cell death in response to global stresses (Portt et al., 2011). Inflammatory cells, signaling about stress, as usual, cause either “arrest” (blockage)) of cell cycle or apoptosis, in dependence on severity of the impact and ability of a cell to reparation. Often stress also leads to re-organization of nucleus architecture, reflecting by

this simultaneously, inhibition of important nuclear pathways (for example, replication and transcription) and activation of specific response reactions to stress (for example, reparation of DNA). In some cells nucleolus is the central node of coordination of reaction to stress (Boulon et al., 2010).

Last studies show (Nakabeppu et al., 2010) that in conditions of oxidative stress accumulation of oxidized nucleoside three phosphates such as 8-oxo-dGTP in the nucleotide pool, is the main process causing cellular disfunctions, including apoptosis and ageing. MutT-homolog-1 (MTH1) and liked with it enzymes are existed to counteract this process in mammalian cells. Expression of MTH1 plays a significant role in apoptosis and participates in the opposing to neurodegeneration. Apoptosis and aging are closely linked with Nrf2-Keap1 signaling system (Surch, 2004) and the second phase of detoxification enzymes (Gao et al., 2004), whose expression is correlated with MAPkinases and proteinkinase C. This makes it possible to trace a more complicated pathway of antioxidant and regulatory zinc effects (Figure 3).

Intracellular ROS are generated as side products of metabolism in aerobic conditions, through mitochondrial respiratory chain, which includes 4 complexes (I-IV), coenzyme Q and CytC. Extracellular ROS are the products of biotransformation of xenobiotics and drugs, inflammatory processes, UV- and ionizing radiation etc. (Al-Guborya et al., 2010). Low level of ROS may function as a messenger of redox-active signaling, while, high level of ROS causes damage of cells (Yu et al., 2006).

Main components of ROS are superoxide-anion, hydrogen peroxide, hydroxyl radical and peroxynitrite, forming from NO in oxidation. Free radicals able to cause changes in DNA sequence and may activate proto-oncogenes and/or inactivate genes- supressors of tumors. Thus, ROS are involved in the process of apoptosis and in pathogenesis of cancer (Radyuk et al., 2004), and in adaptative process of the organism.

Antioxidant system, which protects the organism from action of ROS, includes a set of compounds such as ICDH and G6PD, NADP/NADPH, Gsr, Gpx, GSSG/GSH, catalase, SOD et.. Significant part of their ways of action is linked with zinc ions (mainly, due to inhibition or increasing of corresponding genes expression). For example, RPE cells can actively uptake zinc through the transporter Zip2, and the increased intracellular zinc upregulates the Nrf2-dependent antioxidant function (Rezaei et al., 2008).

At present time, numerous studies are devoted to process of ageing. In this functioning of antioxidant system are considered, for example, at rodent models (Hindle et al., 2010), where it was shown, that there is increasing of CAT and Gpx levels with age. Also a growth of SOD level (at 25-50% in dependence on the animal species) and marker of lipids peroxidation is observed.

4.1 Cu, Zn-Superoxide Dismutase

Cu, Zn-superoxide dismutase (SOD) is a one of the key enzymes, participating in the apoptosis and having the zinc ion as a cofactor, which is able to cleave superoxide - anion and thereby decreasing by such a mode of action the oxidative stress, arising in the organism (Frohlich et al., 2001). As a result of dismutation reaction hydrogen peroxide and oxygen in triplet state ($^{T}O_2$) are produced. So, development of the oxidative stress is linked often with zinc deficiency (or leads to it) in the organism or in the food that was demonstrated at different types of cells and organisms (Hidalgo et al., 2002).

At the present time, when a significant use of nanomaterials is observed, in particular, of ZnO nanoparticles, then it is necessary to take into account that the oxidative stress is considered to be a one of the main harmful consequences of their action on humans (Shvedova et al., 2010; Sharma et al., 2009). Last investigations were devoted to their geno, cytotoxicity in combination with other factors that may be very dangerous (Yin et al., 2010). Besides, due to their extremely small size there is an anxiety by the fact that they may interact directly with macromolecules, such as DNA, increasing apoptosis of normal cells. Nanoparticles of ZnO caused the oxidative stress in cells with depletion of glutathione, catalase and SOD. Even at low concentrations such particles possess genotoxic potential, moreover, a dependence of toxic effect on the dose and form of the particles have been observed. However, it was possible to use these properties of ZnO nanoparticles for induction of preferable apoptosis of cancer cells (Premanathan et al., 2011).

An oxidant defence system, including zinc ions, works through different mechanisms (Powell, 2000), such as sulfhydryl protection from oxidation, induction of MT-proteins, and also through intracellular and extracellular SOD. Moreover, zinc is capable to replace redox-active metals (Cu and Fe) at membrane-binding sites. In this connection, zinc inhibits lipid oxidation in liposomes to prevent copper and iron binding with negatively charged phospholipids (Zago et al., 2001). Combined action of zinc with other lipid-soluble (α-tocopherol) and water-soluble (epicatechol) antioxidants in prevention of Fe^{2+}-induced lipid peroxidation is known.

For WT SOD a nucleolytic activity was revealed (Jiang et al., 2006), which was linked with inclusion of exogenic bivalent metals, such as magnesium and manganese, in the enzyme-DNA complex. Such a complex may provide a site of low and high affinity to a metal ion, i.e.WT SOD uses a mechanism, in which both ions directly take part in the process of catalytic cleavage of DNA (Jiang et al., 2007).

Together with catalase, SOD may be considered as a first line of cell protection from the oxidative stress products. SOD behavior is actively studied at different types of organisms to reveal reasons of its expression and determination of gene domains, which regulate this enzyme (Cioni et al., 2003; Estevez et al., 1999). In humans appearance of additional amount of zinc or, on the contrary, its deficiency may influence on SOD1 in a cytoplasm (dimer) and extracellular SOD3 (tetramer). In study of WT SOD and two mutant forms (Met40Glu and Lys24Asn), carrying a negative charge at amino acid clusters at the border of dimer formation, from *Photobacterium leiognathi* (PSOD), deficiency of Cu and Zn leaded to dimer dissociation with formation of monomers. However, it was to possible to restore the dimer in addition of zinc (Cioni et al., 2003).

A key issue is understanding of molecular basis of communication between metal-containing centers and association of subunits, because loss of zinc in WT- and mutant enzymes is associated with ALS and FALS, diseases, linked with apoptosis of motor neurons (D`Orazio et al., 2000). FALS may cause missence mutations in a gene, coding SOD1 (chromosome 21q). Taking into account that WT SOD1 is able to take part in enzymatic reactions, which may be harmful for cells, for example, in lipid peroxidation and nitration, than it is probable, that many SOD1-mutations, linked with FALS, increase a possibility of the enzyme participation in these potentially dangerous functions (increasing of a number of hydroxyl radicals of additional nitrogroups in tyrosine residues) in cell proteins. These peroxidase reactions and reactions of nitration depend on the degree of copper and zinc binding to the enzyme (Estevez et al., 1999).

It is important that substitution of Trp73 residue, localizing at the border between subunits, by Tyr or Phe leads to metal-dependent association of SOD subunits (Cioni et al., 2003). Oxidation of Trp32 is a decisive factor also for H_2O_2/HCO_3^- - dependent covalent aggregation of human SOD1 (hSOD1) (Zhang et al., 2004). Thus, one of the zinc effects on apoptosis is mediated through conformational state of Cu,Zn-SOD (dimer-monomer).

Rates of metals releasing in unfolding of human WT SOD1 (Figure 4) and conformational changes in the core of β-cylinder of the enzyme, which are controlled using intensity of Trp fluorescence, were determined (Mulligan et al., 2008). They were comparable with rates of zinc and copper releasing. The model of unfolding includes firstly dimer dissociation and zinc release, which proceed simultaneously, then slow changes of conformation in the protein core followed by prompt release of copper.

It was shown (Komura et al., 2000), that SOD, added to extracellular medium, may protect cells from damage as a result of UV-exposition. Apoptotic death in murine fibroblast cell line, preliminary exposed to UV (λ=312 nm, 480 мJ/cm^2), correlated with amount of lactate dehydrogenase (LDH), released into the medium (that characterized cell damage), and treatment of culture medium with 0.1-0.3 μM of SOD leaded to inhibition of the process.

SOD1 is offered as a drug in liver fibrosis, which is a peculiarity of chronic infection caused by hepatitis C virus (Emerit et al., 2005). TGF-β1 occupies a distinguished position among different cellular ways of the fibrosis development. Studies on radiation-induced fibrosis showed that SOD1 effectively promotes its reversibility, decreasing TGF-β1 expression (Elchuri et al., 2005).

An epithelium of a respiratory system, in particular, is vulnerable to action of oxidants, either external or if produced in the body, which are arisen in inflammatory cells in acute or chronic inflammation of respiratory ways (Wright et al.,1994). Zinc deficiency leads to the oxidative stress increasing in lungs and decreasing of immunity (Taylor et al., 1997). If zinc is added to ration of nutrition, then the damage from hyperoxia is annulled. Some of antioxidant abilities of zinc are linked with stabilization of sulfhydryl structures and membrane lipids (Carter et al., 2002) and suppression of NO-production (Cui et al., 1999).

Hyperexpression of SOD provides protective function in case of external influences, for example, against dopamine cytotoxicity of neurons (Dumay et al., 2006) and may temporarily inhibit or disrupt autooxidation caused by dopamines, increase the glutathione level, that afterwards prevents activation of apoptotic way and subsequent death of cells. However, such a hyperexpression is not able to protect cells from hydrogen peroxide. Hyperexpression of SOD1 in monocytes blocks inhibition of cell growth and apoptosis, induced by ROS and makes cells to be resistant to toxic action of TNF-α, which decreases SOD1 mRNA, protein and promoter activity (in U937 cells), acting through JNK/AP-1 signaling pathway (Afonso et al., 2006).

Action of inhibitors of SOD may be of particular interest and indefinite. So, TNF-α and etoposid (which produce ROS promptly and in large amounts) and inhibitor of SOD - diethylthiocarbamate (DDC) were used to study ROS in HeLa cells. It was shown (Dumay et al., 2006), that DDC significantly inhibited activation of caspases, loss of mitochondrial membrane potential ($\Delta\Psi_m$) and death of cells, induced by TNF-α and etoposide. But DDC does not inhibit Bax and CytC – translocation and, on the contrary, it is able to cause their changes without alteration of $\Delta\Psi_m$. Thus, DDC has, at least, two antagonizing functions of apoptosis regulation, inducing ROS-dependent translocations of Bax and CytC (potentially

pro-apoptotic), and, at the same time, inhibiting activation and activity of SOD, loss of ΔΨm, and cell death, in ROS-independent cases.

Expression of SOD1 and its enzymatic activity (as well as of Mn-SOD) is decreased in normal as well as in psoriatic fibroblasts in addition of retinoic acid (RA), that makes it possible to use RA as down-regulating agent of these enzymes in treatment of psoriasis (Gerbaud et al., 2005).

It is interesting, that recent studies showed absence correlation between specific diseases of newborns and activity of antioxidant enzymes (Loui et al., 2010).

4.2 Hydrogen Peroxide

The role of hydrogen peroxide in the organism is various and in full depends on its concentration. H_2O_2 is a substrate for a set of antioxidant enzymes and CAT is the main enzyme among them. Hydrogen peroxide is noticeable in process of apoptosis, being a side product of NOX-dependent transport of electrons across membrane of phagosome. In some approximation it is a signaling system, inactivating tyrosine phosphatase that leads to stimulation of cells by growth factors and cytokines and by this way influencung on apoptosis.

Cells, which received apoptosis signal through action of hydrogen peroxide, demonstrate significant decrease of superoxide radical concentration, that is linked with reduction of intracellular medium and is determined by increase of GSH/GSSG ratio and decrease of intracellular pH value (Cleement et al., 1998). It may be said that reductive, but not oxidative stress, is a signal for H_2O_2-mediated apoptosis.

H_2O_2 is able to decrease expression of anti-apoptotic Bcl-2 without changes in expression of pro-apoptotic Bax, and, as a result, the relation of Bcl-2/Bax is decreased (Kilari et al., 2010). Epithelial cells, treated by 200 μM of hydrogen peroxide (H_2O_2) demonstrate during 24 h (Wu et al., 2010) decreasing of viability and become apoptotic with corresponding increase of Bax, decrease of Bcl-2, activation of caspase-3 and release of mitochondrial CytC.

Accompanying presence of zinc and BPDS inhibits H_2O_2-induced of caspase-3 and restores relation Bcl-2/Bax. However, effects of zinc or BPDS made one by one do not influence on these apoptotic markers (Kilari et al., 2010).

Cancer cells are not able to develop and perish in oxygen-riched medium. Toxicity of hydrogen peroxide to cancer cells suggests that H_2O_2 damages their metabolism. So, there are suggestions regarding usage of H_2O_2, as secondary messenger, which may be determined with help of genetically coded fluorescence indicator, for example, HyPer, in real time mode (Belousov et al., 2006). It is known that tumor resistance to action of drugs (in particular, to action of H_2O_2) is often linked to DN-mutations of p53 however it was possible to overcome this using SNP to increase toxicity independently from p53 status (Gomez-Sarosi et al., 2010).

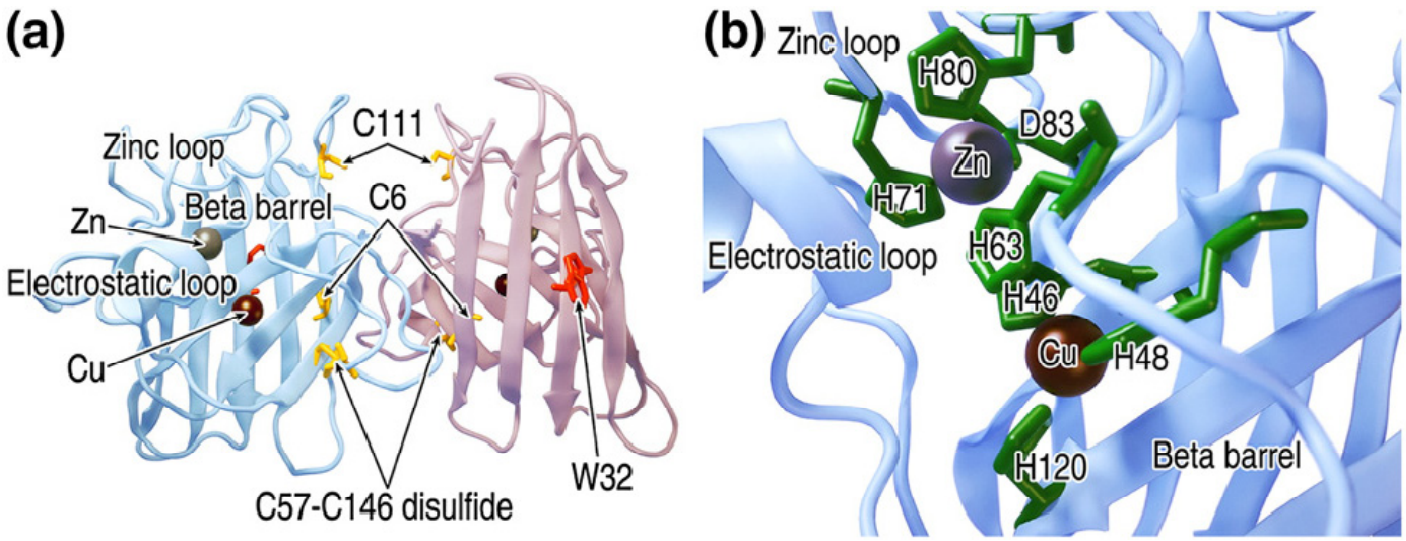

Fig. 4. Structure of human WT SOD1
(a) SOD1 is a homodimer of two 153-amino acid containing subunits, shown in blue and lilac color. Fore Cys residues of WT-protein (yellow color) are close to the surface of dimer joining.
The only exposed outside Trp residue (orange color) is situated on β-cylinder.
(b) Each SOD1 monomer binds one atom of copper and one atom of zinc, which are coordinated by six His residues and Asp residue. Although most of copper-binding residues are situated on SOD1 β-cylinder, zinc-binding residues are in zinc loop (residues 49-82). Electrostatic loop (residues 121-143) forms a part of the active site slit.
Source: Mulligan et al. (2008)

A role of thiol-containing redox-proteins-thioredoxine, peroxiredoxine and Grx is tightly linked with hydrogen peroxide function and, as whole, with ROS, which take part in maintenance of cellular redox-homeostasis and redox-dependent regulation of some intracellular processes, including proliferation, differentiation and apoptosis (Kalinina et al., 2008). These proteins combine antioxidant properties and ability to activate transcription of genes, including genes, coding antioxidant enzymes as well as to inhibit redox-dependent ways of apoptosis activation (including those with zinc ions involvement). Thus, the struggle with consequences of ROS is made by complicated and interlaced ways.

Action of Grx is conjugated with function of glutathione reductase and GSH/GSSG ratio, which is an indicator of cellular redox-status, correlating with biological status of a cell. It is known that in apoptosis redox-potential reaches 170 mV (in proliferation – 240 mV) (Schafer et al., 2001). Grx catalyzes formation and reduction mixed disulfides (Yoshitake et al., 1994). There are three isoforms of Grx in humans: cytosole Grx1 (12 kDa) with active center CPYC and two mitochondrial Grx2 (14 kDa) with active center CSYC and Grx5 with active center CGPS (Schafer et al., 2001), in this Grx2 has two splicing forms α and β, localized, correspondingly, in mitochondria and nucleus. Grx1 is able to restore (by way of deglutathionilation) functional activity of some proteins, including creatine kinase, c-Jun, protein tyrosine phosphatase 1B and caspase-3 (Davis et al., 1997), which participation in the apoptosis and, sometimes, activity indirectly depend on zinc ions concentration, that in some cases must cause “conflict of interests” and possibility to change a decision regarding apoptosis after receiving of a signal about its beginning.

It is important that expression of GLRX1 gene is sufficiently increased in tumor cells and Grx2 suppresses apoptosis preventing releasing of CytC out of mitochondria (Lilling et al., 2004). In general, the function of Grx2 is not clear. Evaluation of its anti-apoptotic function (Wu et al., 2010) by studying its ability to protect complex I in mitochondrial electron-transport system of epithelial cells, showed, that hyperexpression of Grx2 may protect cells from H_2O_2-induced damage (leading to apoptosis), while Grx2-knockdown (KD) demonstrates an opposite effect.

Acute H_2O_2-mediated oxidative stress in endothelial cells of pulmonary artery is linked with elevation of intracellular zinc that is one of key events linked with disruption of functions of mitochondria and induction of apoptosis (Wiseman et al., 2007).

In burns not balanced antioxidant response is possible (Agay et al., 2005) that in part is also linked with hydrogen peroxide. In this the level of zinc is decreased in the blood serum after 6 hours, and in two stages is increased in the liver simultaneously with elevation of SOD (from 6 hours to 4 days), and re-distribution of zinc and copper is observed there (in the absence of changes in muscles and brain). In this, activities of Gpx and SOD were only significant in the blood plasma.

H_2O_2-generating system Glu/GO, which induces DNA fragmentation, may be inhibited by zinc (50 μM) in combination with BPDS (2.5 mM) (Kilari et al., 2010). Moreover, combination of zinc and BPDS, is able to restore the GSH/GSSG ratio, increasing expression of DMT1, a transporter of bivalent ions of metals.

Mechanisms, participating in elevation of ROS and RNS during decreasing of cellular zinc, are not studied in full. Induction of oxidative stress by zinc deficiency includes short-term as well as long-term mechanisms, where ways of zinc and hydrogen peroxide are interlaced. The reason for such a short growth of cellular ROS may be linked with NADPH-oxidase

involvement in the process (Oteiza et al., 2005; Beckman et al., 2001). In the long-term perspective a requirement in zinc as physiological antioxidant plays a role; during changes of functions of mitochondria, leading to increasing of production of ROS or hypoxia; disruption of expression of components of the respiratory chain; and alteration of activity/expression of enzymes, which participate RNS/ROS metabolism.

Hypoxia and extracellular inflammatory signals may induce intracellular accumulation of ROS. It is necessary to notice in this connection a role of PGC-1α, which may induce mitochondrial biogenesis that leads to increasing of oxygen consumption and decreasing of its intracellular availability for HIF-hydrolases. This, in turn, stabilizes HIF-1α in hypoxia, which in normal conditions (in normoxia) is degraded through ubiquitin-proteasome way after binding with pVHL protein (O`Hagan et al., 2009). Intracellular ROS-stimulation is able to provide releasing of IκB of proteasome degradation that allows NF-κB to enter the nucleus, bind with elements of DNA control in order to induce gene expression. So, it is possible to consider ROS as a secondary messenger of signaling pathways regulation, which control gene expression and post-translational modifications of proteins (Allen et al., 2000; Valko et al., 2007). It is in prospect to reveal the precise role of zinc at these stages, but, no doubt, that the role of ^{67}Zn magnetic nucleus (see Chapter 9) will be of particular significance.

4.3 Zinc and Caspase Cascade

Caspases are proteolytic enzymes with cysteine residue in the active center (ICE-like cysteine proteases), and this makes them susceptible targets for transition metals (Xu et al., 2001), including zinc. Studies *in vitro* demonstrated that caspases-3, -6, -7 and -8 are suppressed by zinc in concentrations lower that micromolar, they are not inhibited by calcium in concentrations lower than 100 мМ (Stennicke et al., 1997; Maret et al., 1999). Increasing of concentration of intracellular zinc due to usage of pirithione, the zinc ionophore inhibits activation of caspase-3 that indicates a possibility of direct involvement of zinc in apoptosis in neuroblastoma cells (Ho et al., 2000). Use of pyrithione and $ZnSO_4$ inhibits H_2O_2-induced activation of caspase-3 however addition of TPEN (and, correspondingly, exhaustion of labile zinc) causes increase of caspase-3-dependent apoptosis by way of activation of caspase-3 through ROS (Truong-Tran et al., 2000, 2001; Carter et al., 2002). Results of apoptosis in HL-60 cells is suggested the possibility of inhibition by zinc ions of processing of a precursor to caspase-3 (Aiuchi et al., 1998).

On the contrary, zinc does not inhibit activation of caspases -8 and –9, caused by treatment of cells with TNFα or etoposide (Chimienti et al., 2001) or CytC release from mitochondria.

It is considered that activation of caspase-3 is one of early markers of apoptosis. Zinc completely inhibits activation of caspase-3-, -6- и -9, in ricin-treated cells U937, when these cells were treated by solution of $ZnCl_2$ (Tamura et al., 2002), however, zinc blocks process of activation of these caspases, but do not perform direct inhibition of the enzymes. Zinc deficiency increases activation of caspases in rat embryos (Jankowski-Henning et al., 2000). Because metalloproteases use zinc ion to catalyze hydrolysis of peptide bonds, than most metalloprotease inhibitors contain zinc-binding ligand of thiol, of hydroxamate type etc. Structures of caspase inhibitors are considered in a review (Madala et al., 2010). An interesting method to monitor the apoptosis by way of watching proteolytic activity of caspase-3 is offered on the basis of usage of semi-conductor quantum dots, which nanosize and unique optical properties made them very attractive subjects to be used as a layer for photoluminescent biosensor (Prasuhn et al., 2010).

4.4 Zinc and NO

Nitrogen oxide is a physiological factor, which is able to initiate the apoptotic program in cells, is one of the key signalling molecules, regulating functions of cardiovascular, nervous and immune systems of the organism. A unique chemical nature and a large amount of intracellular targets for NO and its physiologically active redox forms, keep the question opened how the damaging action of the nitrogen oxide on cells is mediated. However, it is obvious that is a consequence of multitude interactions with other molecules, such as ROS, metal ions and proteins.

Mitochondrion is a main generator of free radicals (Curtin et al., 2002). In physiological conditions electrons transfered through electron-transportation (respiratory) chain may in some cases together with oxygen generate $O_2^{\cdot -}$. Another source of $O_2^{\cdot -}$ are enzymes such as cytochrome P-450 in ER, lipooxygenase, cyclooxygenase, xanthine oxidase and NADPH oxidase. Action of SOD leads to H_2O_2 formation, which may than react with Fe^{2+} with formation of hydroxyl radical in Fenton reaction. However, the hydroxyl radical may be formed in catalyzed by metals Haber-Weiss reaction. Formation of superoxide radical and hydroxyl radical may furher lead to formation of different peroxides, including peroxynitrite, the strongest cytotoxic agent. The rate of NO interaction with superoxide radical is very high ($6.7\ 10^9\ M^{-1}s^{-1}$) (Sawa et al., 2010). In the same time, NO make brake oxidative processes, provoked by formation of oxyferryl radicals. Reactive nitrogen-containing intermediates (RNI) are active and important products for apoptosis. NO is formed as endogenic product in oxidation of L-arginine into L-citrullin in the presence of NADPH-dependent NOS and exists in various chemical forms (NO^-, NO^+ и $NO^{\cdot}$), having wide degree of chemical activity and functions. To activate eNOS it is necessary to use calcium and calmodulin.

Some of antioxidant properties of zinc are linked with suppression of nitrogen oxide production (Cui et al., 1999).

Influence of NO on apoptosis proceeds with help of caspase-3, which, while being in nitrosylated (at Cys in the active center) state is less active and limited proteolysis plus denitrosylation are needed to be done to activate the enzyme. So, the nitrosylation/denitrosylation reaction is one more mechanism of intracellular signaling, which is involved in initiation of the caspase cascade. However, direction of these processes depends on the NO and zinc concentrations in a cell (Sawa et al., 2010). Classic NO signaling pathway includes formation of a secondary messenger cGMP and runs through redox-sensitive thiols which are targets for NO and form conjugates with it. However, they also serve as targets for zinc.

Obviously, influence of NO on apoptosis is in most cases a mediated process (in particular, by zinc) and depends on concentration and a cell type. In some types of cells NO may promote apoptosis, but in other cells, on the contrary, it is an inhibitor of apoptosis. In hepatocytes NO inhibits caspases, the main mediators of the cell death. Low physiological concentrations of NO may inhibit apoptosis, but more high concentrations become toxic for cells, inducing their death as a result of apoptosis or necrosis. Long exposition to NO, for example, in chronic inflammatory states, may predispose cells to tumor development through DNA damages.

It was shown (Wei et al., 2000) that exposition of nervous cells to donors of NO (for example, with SNAP) induces apoptosis through activation of ROS and accumulation of extracellular H_2O_2 and products of lipid peroxidation, while their preliminary treatment by

acceptors of free radicals or by SOD inhibits apoptosis. Zinc as an antioxidant may also decrease toxic effects of NO. Studies of the regulation of damage of immobilized human keratinocytes and their apoptosis induced by NOS, intracellular free zinc ions and UV - radiation, showed, that UV causes elevation of intracellular zinc concentration, that depends on increasing of activity of cNOS and superoxide production (Wang et al., 2010). Removal of zinc with help of a small concentration of TPEN did neither cause cells death nor prevent their UV-induced apoptosis. Nevertheless, increasing of TPEN concentration up to 50 μM induced cytotoxicity. Treatment of cells with membrane-penetrating superoxide dismutase (PEG-SOD) reduced apoptosis of cells during exposition to UV. Thus, the relationship between activation of NOS and increase of zinc concentration exists, and the role of cNOS in regulation of oxidative stress and apoptosis during UV-radiation is not completely understood.

Nitrosative stress may critically change zinc mobilization. Nitrogen oxide and peroxynitrite promote zinc release from metallotioneins by *in vitro,* as well as *in vivo* interaction predominantly with MT-3 (Frederickson et al., 2002).

DNA damage, protein modifications, p53 activation and inhibition of mitochondrial respiration promote NO-mediated apoptosis through mitochondrial and Fas- receptor pathways. Multiple cellular protective systems including GSH, antioxidant enzymes and Nrf2-Keap1 signaling pathways participate in cell response to decrease the damage from toxic levels of NO (Sawa et al., 2010).

5. ZINC EFFECTS ON BRAIN CELLS APOPTOSIS

There is the highest zinc concentration in the brain tissue in comparison to other tissues. It was calculated that average total concentration of zinc in brain tissue is about 150 μM that is ten-fold higher than in the blood serum (Takeda, 2000). However, the concentration of free zinc ions in a cytosole is supposed to be subnanomolar, i.e. ~ 500 nM in extracellular fluid of brain (Weiss et al., 2000), and in neuronal cells concentration of free zinc ions should be maintained in fM levels, that is due to extrusion, buffering and isolation (Frazzini et al., 2006).

On the contrary, content of zinc in synaptic vesicles of some neuronal cells of anterior of the brain more than 1 mM (Frederickson et al., 2000). Neurons of the anterior brain represent a group excitatory glutamate- or glucose-ergic neurons. Neuronal cells, which contain free zinc ions in vesicles, so-called zinc-enriched neurons (ZEN), present also in other brain regions. In bone marrow the majority of ZEN termini are inhibitors of γ-aminobutyric acid (Mocchegiani et al., 2005). Because ZEN neurons are unevenly distributed, than distribution of zinc in the brain tissue is irregular. The highest concentrations are presented in such regions of the anterior brain as hippocampus, cerebellar tonsil and neocortex (Frederickson et al., 2000).

There are three main functions of zinc in the brain: vesicular, localized in synaptic vesicles of nerve endings; membrane-bound and as free ions in the cytoplasm. Neuron dendrites concentration of Zn by factor of 2,5–3 is higher due to its presence in the vesicular fraction, from which it goes to synaptic slit in electrostimulation and may change activity of various neuromediators, which regulate activity of stimulatory and inhibitory receptors (Osipova et al., 2005). Zinc may act as neuromediator in stimulating synapses and plays significant role in response to stress and in functions of zinc-dependent enzymes, which provide compensatory abilities of brain.

Mechanisms that modulate the pool of free zinc, is crucial for brain health preservation and its productivity.

Transport of zinc to brain parenchyma proceeds through system of brain barriers: blood-brain (BBB) and blood-cerebrospinal fluid (Takeda, 2001). Vascular plexus of a brain stem is a main place where heavy metals penetrate through blood-brain barrier and where neuroprotective action of zinc is realized. Transfer of zinc to positions, which regulate its penetration-absorbtion through systems of BBB, proceeds through binding with His residues of zinc transporters in the blood plasma and in spinocerebellar fluid (Takeda et al., 2002). In order to maintain zinc homeostasis, brain capillary endothelial cells react on changes in the zinc status, increasing zinc uptake in the presence of low zinc concentrations in the blood and decreasing the uptake in the presence of high concentrations (Lehmann et al., 2002).

It is suggested, that two main mechanisms may explain zinc ions gradient formation on plasmatic membrane (Sekler et al., 2007; Sensi et al., 1997) – this is a primary ATPase pump; and a secondary active mechanism of sodium gradients usage. However, in case of mammals there are no proofs of such a gradient existence yet, although the gradient was observed in bacteria (Banci et al., 2002), and in *Arabidopsis*. Moreover, it is necessary to account significantly expressing in the brain zinc transporters: ZnT-1 and ZnT-3, able to decrease Zn-toxicity, in particular, by way of its loading to synaptic vesicles (Chao et al., 2004). Specific channels such as calcium potential-dependent channels of L-type (Colvin et al., 2000), $Na+/Zn^{2+}$ ion-exchangers, NMDA-receptor-dependent channels and Ca^{2+}-permeable AMPA/κainate channels (Ca-A/K channels) (Palmiter, 1998) may be mediators of neuronal absorption of zinc. On the contrary, zinc transport proteins belonging to ZnT family regulate flow of zinc from neurons, and also vesicular absorption of zinc (Seve et al., 2004).
In central nervous system, zinc involved in regulation of many channels and receptors, may act as a trigger for neurons loss (Mantyh et al., 1993). Effects of high concentrations of zinc *in vitro,* as well as *in vivo* promote death neurons, and in the same time elevated neuronal concentrations of zinc linked to loss of neurons, are observed in exciting and toxic conditions such as epilepsy, ischemia and craniocerebral injury. Interleukin-1β-converting enzyme (ICE), free radicals and cell cycle kinases are among mediators of neurons apoptosis (Rubin et al., 1994).

Physiological role of synaptic zinc is relatively little studied, but synaptic vesicles of some glutamateergic endings contain a high concentration of zinc and it is considered that it participates in modulation and release of glutamate, γ-aminobutyric acid (Takeda et al., 2003) and, probably, in modulation of glyceroergic synaptic transmission (Laube, 2002). Glutamate is a main stimulatory transmitter, acting in CNS, which makes prompt effect by interaction with ionotropic (ligand-dependent ion channels) and glutamate receptors (mGluRs). Zinc-binding sites with high and low affinity were revealed in NMDA-receptors and may directly to modulate of receptor-mediated excitatory postsynaptic currents (Mocchegiani et al., 2005). With use of gene chips, hundreds of genes were revealed which differentially are expressed in response to NMDA-stimulation or synaptic activity in the culture of hippocampus neurons (Zhang et al., 2007), and functional analysis of some of these genes leaded to revealing of Bcl6 and Btg2, as new neuronal survival genes (Portt et al., 2011).

Zinc performs modulation activity not only by direct binding with post-synaptic receptors, but also, in the difference from usual neurotransmitters, entering post-synaptic neurons (Burdett et al., 2003). It is suggested (Frazzini et al., 2006) that loss of neurons linked with zinc cytotoxicity may be provided by harmful trans-synaptic movement of the cation from zinc depot to postsynaptic neurons, so-called "Zn(II)-translocation".

A hypothesis exists concerning zinc release by free diffusion into intercellular space in the process of exocytosis. However, it was shown (Nydegger et al., 2010), there is no such a free zinc flow, but it appears in the intercellular space and is detained by various binding ligands. Such a process was named as "externalization" and it needs further studying.

Sympatic neurons in culture die from apoptosis, when they are deprived of NGF. If to introduce SOD, or express vector, containing, SOD cDNA, then apoptosis will be delayed. This delay is like those observed in introduction Bcl2 expressing vector. If to introduce SOD in 8 hours after deprivation of NGF, no protection from apoptosis is observed (Chao et al., 2004).

Human senescence marker protein 30 (SMP30), which functions as like lactonase and hydrolyses different carbohydrate lactones, is able to hydrolyse material of nerves. Its expression decreases independence of androgen in ageing cells and it influences on calcium homeostasis. Only one atom of a metal, most probable of calcium or zinc, is situated in the active center of SMP30. Calculated k_{cat} demonstrates preference for bivalent cations in the order $Zn^{2+} > Mn^{2+} > Ca^{2+} > Mg^{2+}$ (Chakraborti et al., 2010).

Zinc has many-directed influence on cell physiology and may activate several death ways in neurons, because it modulates necrosis as well as apoptosis (Kozlowski et al., 2009). This may also be linked with non-mitochondrial way of ROS generation, in which neuronal nNOS is involved (Spahl et al., 2003).

Extra-mitochondrial and mitochondrial ways of neurons death may meet. Mobilization of intracellular zinc in conditions of oxidative stress may provide the link between necrotic and apoptotic pathways. Mobilization of zinc by cell oxidants in intact neurons effects on mitochondrial membrane potential while in isolated mitochondria, similar zinc growth initiates opening of mPTP (Kim et al., 2000). Induced by Zn mitochondrial generation of ROS promotes further releasing of zinc. It is supposed that both pathways may work jointly to damage neurons.

Action of powerful source of ROS – natural antibitiotics streptozotocide which is capable to cause diabetes mellitus in experimental animals – at the brain level influences hippocampus and cerebellum. In these conditions introduction of zinc leaded to decreasing hyperglycemic status occurrence, linked with elevation of expression/production of MT (Beltramini et al., 2006).

It is considered that zinc-induced neurotoxicity is in the basis of deterioration of nigrostrital dopamineergic system in patients with PD (Lin et al., 2003), studying of which *in vivo* showed zinc translocation in nigral cells after intranigral injection of zinc ions. Zinc-induced growth of lipid peroxidation and cytosole CytC, and also reduction of content of striatal dopamine in infused substance nigra may be prevented by application of vitamin D3. Moreover, vitamin D3 hampered zinc-induced oxidative damage in the rat brain.

MT-proteins play an important role in the brain, actively participating in the intracellular zinc turnover (Mocchegiani et al., 2005). In the last time more data support the suggestion that damage of mitochondria, and, correspondingly, mitochondrial ways of neurons death, become the main factor of neurodegenerative diseases development (Dua et al., 2010). Mitochondrial dysfunction includes DNA-mutations, disruption of mitochondrial redox-potential and, that is sufficient, decrease of mitochondrial ATP production (Swerdlow, 2002; Banerjee et al., 2009). Mt-DNA-mutations are responsible for dis-regulation of Ca-

homeostasis in mitochondria in AD (Damiano et al., 2006), PD (Faust et al., 2009), ALS (Martin et al., 2009) diseases. But, certainly, increasing of ROS generation (or decreasing of antioxidant response, correspondingly) is a one of main damaging factors and, consequently, any disruption in the structure and/or expression of SOD1 may be crucial for such diseases.

In cases of the neuronal differentiation and proliferation processes, energetic factors attract particular interest at present time (Rafalski et al., 2011). Thus, in such energy-sensitive enzymes as AMPK and Sirt-1, both low [AMP]/[ATP] and [NAD+]/[NADH] ratios were found increasing which, in turn, promotes an activation of AMPK leading to the [NAD+] synthesis rate elevation along with a consequent activation of Sirt-1. Sirt-1, deacylating substrates, includes histon and transcription factors. However, function of Sirt-1 in differentiation of neuron stem cells (NSCs) is modulated by oxidation state, that determines the way of differentiation either to neurons (in case of inhibition of Hes-1 expression) or to astrocytes (in oxidation conditions). Since zinc is able indirectly influence on ATP synthesis and oxidative stress, then it is quite probable that it influences processes of cell differentiation and apoptosis in the brain through the above mentioned mechanisms.

Expression of SOD1 is registered in NSCs postnatal subventricular zone and some other compartments (Faiz et al., 2006), as it is considered to maintain ROS balance (Madhavan et al., 2008). There are evidences for role of ROS as a regulator of balance between self-reproduction/proliferation and differentiation of stem cells into progenitor cells of oligodendrocytes, hematopoietic cells and NSCs (Lekli et al., 2009).

5.1 Zinc and Alzheimer's disease

It is considered that Alzheimer's disease (AD) is a proteinopathy, i.e., disease linked with accumulation of incorrectly folded proteins in brain tissues: either β-amyloid (amyloid hypothesis) or tau-protein (tau hypothesis) (Hashimoto et al., 2003). Senile plaques (Ohnishi et al., 2004) or neurofibrill coils of tau-protein are formed inside neurons with subsequent collapse of transport system in the neuron, disruption of signal transduction between cells and cell death (Igbal et al., 2005), i.e., a neuronal degradation is observed. Inflammatory processes and cytokines may play a role in its pathophysiology and, consequently, the role of zinc must be significant. It is known that amount of zinc in the blood plasma decreases from birth to old age however, in comparison with the norm the greater deficiency of zinc is observed in plasma and spinocerebellar fluid in patients with AD (Baum et al., 2010), which may influence on providing of the brain tissues with this ion. However, in the same time an excessive capture of zinc ions by senile plaques is observed (Duce et al, 2010). Such hystochemically reactive deposits of zinc were found to be specifically localized in amyloid angiopatic accumulations and neurofibrillar coils (Friedlich et al., 2004). In the last time coordination chemistry of zinc complexes with β-amyloid peptide is studied in detail (Faller et al., 2009) and apparent dissociation constants were determined in the range (in dependence on conditions) from 1 to 20 mM.

Amyloid β-peptide and A2M, participating in the development of neurodegenerative processes, are able, besides MT, to absorb zinc in ageing brain. Deposits arise also in normal ageing, but their formation is facilitated in case of neurodegeneration and proceeds, namely, in the brain regions enriched by zinc. So, disruption of zinc binding in the brain is considered as one of AD promoters. However, studies, performed in Alzheimer's region of hippocampus demonstrated (Mocchegiani et al., 2005), that MTF-1, expression of which is

directly linked with availability of intracellular zinc, is decreased simultaneously with decreasing of MT-3 expression. Levels of ZnT1, ZnT4 and ZnT6 (Lyubartseva et al., 2009), and also ZnT3 (Adlard et al., 2010) undergo changes in tissues of brain from patients with AD.

In case of neurological disorders, when neurons die from apoptosis, chelated zinc is accumulated in perikarya of neurons before or during degeneration. Thus, there is some paradox between decreasing of zinc in brain of patients with AD and supposed link with abnormally high level of zinc, promoting formation of plaques (Cuajungco et al., 1997). This is explained by suggestion that neuropathological changes in zinc metabolism are mediated by numerous endogenic and exogenic stressors.

5.2 Zinc and lateral amyotrophic sclerosis (ALS, FALS)

ALS (inherited variation FALS) is one of the diseases, associated with motor neurons. It is considered that the next reasons are of importance for its development: disruption of cytoskeleton, which leads to changes of axon transport; toxicity of intracellular protein aggregates, leading to disruption of secondary assembling of cytoplasmic proteins; myoglial activation and alteration of free radicals and glutamate metabolism (Skvortsova et al., 2001a). Multiple studies, devoted to biochemistry of the disease, concern consideration of SOD1 mutations effects. It is considered that one of them, namely, D90A substitution (Asp90Ala) evidently leads to FALS (Skvortsova et al., 2001b). Also under interest the substitution G93A in SOD1, which leads to increasing of peroxidase activity in comparison with WT SOD1 and associates with DNA in the nucleus, initiating mechanism of apoptosis through p53, and participating in this way in pathogenesis of ALS (Barbosa et al., 2010).

At present time more than 100 mutations of SOD1 gene are known, which may participate in pathogenesis of the disease and most of them represent missence-mutations, but nonsence-mutations are also among them. Mutations are situated, mainly, in 4 and 5 exons. It is necessary to note that there is a small amount of mutations (it is not clear) in 3-rd exon, coding site of zinc binding. Clinic consequences of mutations are described in detail in (Formigari et al., 2007; Al-Chalabi et al., 2003; Hand et al., 2003). Many mutations suggest increasing of conformational mobility of SOD1 that leads to formation of population of the enzyme with incorrect folding and new cytotoxic properties (Mulligan et al., 2008). Zinc ion plays an important role in this process, especially its deficiency as a result of more readily release of the metal from the enzyme. Moreover, disruptions are probable in the region of electrostatic loop that may lead to increasing of a number of substrates for such an enzyme (Estevez et al., 1999). Damages of WT SOD1 in the result of oxidative stress also lead to incorrect folding and the enzyme aggregation and, as a consequence, initiation of ALS (Kabashi et al., 2007; Rakhit et al., 2004).

A crystal structure of human Zn-deficient SOD1, that contains two zinc-binding ligands substituted for hydrogen-bonding serine residues, was studied with the aim to evaluate significance of zinc position in SOD1 structure and pathogenesis. This structure revealed 9°-rotation of subunits, and this discloses a SOD dimer surface interface and represents the largest intersubunit rotational shift, observed among human SOD variants. Besides electrostatic loops and zinc-binding subloops were in part disarranged, catalytically important Arg143 was turned out of active center and usually rigid intermolecular disulfide bond Cys57-Cys146 acquired two different conformations. All these changes allow small molecules to have more access to catalytic atom of copper, and this is in accordance with observed increase of redox activity of zinc-deficient SOD. Moreover, dimerization interface is

becomes weak and Cys57-Cys146 disulfide becomes more labile, and this is evidenced by increasing of aggregation of zinc-deficient SOD molecules in the presence of thiol-reducing agents. The most unpleasant event is fast heterodimerization of Cu,Zn-equimolar SOD with Zn-deficient SOD ($T_{1/2}$≈15 min) that prevents aggregation. Stabilization of zinc-deficient SOD, as heterodimeric partner of Cu,Zn-SOD may provide dominant inheritance of ALS mutations (Roberts et al., 2007). Using computer-based screening a new class of characteristic for ALS mutant SOD aggregation blockers is predicted and experimentally tested (Nowak et al., 2010).

The data were obtained that FALS is developed as a result of copper deficiency or impairment in its inclusion in enzyme structure, and this is strongly correlated with zinc concentration and its regulation of the pH function and conformational state of the enzyme. However, absence of correlation between disruption of antioxidant function of mutant SOD1, cause by zinc ion deficiency and FALS development (Yoshitake et al., 1994) was shown. Studies of blood samples of group of patients autosomic-dominant FALS in comparison with control group did not reveal statistically reliable differences in concentrations and specific activities SOD1 (Bowling et al., 1995). Also, it was shown (Subramanian et al., 2002), that blocking of gene, coding a shaperone- transporter of copper ions for SOD-1 (CSS), and, as consequence, changes of antioxidant properties of the enzyme, regulated by copper ion, does not influence on the course of the disease. It is considered that mutant protein SOD1 may not participate in normal intracellular transport due to defects in its tertiary and quaternary structures that predisposes aggregate formation. By introducing in neuronal organelles, the aggregates are able to disrupt their functions as well as ways of degradation of important regulatory cellular factors, in particular, ubiquitin and shaperones (Cleveland, 1999). Degenerative changes in Golgi apparatus in ALS were immunochemically shown (Mourelatos et al., 1993). However, the specificity of changes for this disease as well as the order of involvement in the process of the disease development of Golgi image (primary or secondary) was not revealed.

A strong zinc chelator is structural protein, neurofilament L., which is accumulated in the beginning of degeneration of motor neurons and, possibly, competes with SOD1 for zinc. Experiments on transgenic mice, expressing ALS, linked with SOD1 mutant (so-called ALSSOD-transgenic mice) demonstrate that vulnerability of motor neurons decreases and paralysis is delayed in case of neurofilament L.gene removal. However, hyperexpression of heavy subunits of the neurofilament L. protected ALS-SOD of transgenic mice (Mocchegiani et al., 2005), that evidences about indirect participation of the protein in ALS pathogenesis.

Cellular model of FALS is developed by way of permanently transfecting motor neuron of cells of NSC-34 cell line type with human of wild type (WT) or mutant (G93A) SOD1 (Rizzardini et al., 2005) Presence of G93ASOD1 does not change proliferation of cells, but its toxicity was obvious, when cells were in the phase of growth plateau. Cytometric analysis has shown that at this stage viability of G93ASOD1 is significantly decreased and that the ROS level was significantly higher in the living G93ASOD1 cells in comparison with WT SOD1 cells. Even a small amount of mutant SOD1 moves the motor neurons into the state with oxidative stress and damages of mitochondria, which cause their vulnerability and death.

6. ANTI-INFLAMMATORY PROPERTIES OF ZINC - Zn EFFECTS ON IMMUNE RESPONSE OF THE ORGANISM.

A recommended dose by WHO norm of zinc for adults is a daily dose of 15 mg. However, there are zinc-deficient territories, distinguishing by low zinc content in the environment and in water and food ration, for example, if of labile zinc in soils less than 0.1 mg/kg, and in water and food ration of the population - 9.1±0.9 mg/day (Ukhterova, 2008). For residents of such a region (Ivanov et al., 2008; Karsakova et al., 2008; Ukhterova, 2009) relationship between zinc deficiency and chronic obstructive pulmonary disease was studied. Development of the disease depends on the immune response. Zinc deficiency leaded to presence of preferential hypofunction in the system of T-cell immune response that additionally aggravates effects of other risk factors on the immune system. Peoples having alleles DRB1*11(05) and DQB1*0301, marking low level of indicators of cellular mechanism of immunoreactivity, in their genotype are more sensitive to geochemically caused zinc deficiency and have an increased risk to ill in conditions of its natural deficiency. In this case decreasing of expression at lymphocytes of positive activation markers – receptors for IL-2, transferrin, HLA-DR-antigens at lymphocytes and acceleration of activation process was observed. To control efficiency of treatment, Cu/Zn index is used. It is considered that decreasing of this ratio to value of 1.26 may be considered as positive prognosis feature (Ukhterova, 2009).

Thus, the normal entering of zinc into organism is an important immunoregulatory factor, linked not only with antioxidant, but also with anti-inflammatory role (both factors may intersect), especially in maintaining of homeostasis of epithelial tissues, which are at the front edge to combat infections. Changes in metabolism caused by zinc are observed besides chronic obstructive pulmonary disease, asthma and other chronic inflammatory processes in the respiratory ways (Valle et al., 1993; Fleisher, 1997), when epithelial barrier is the most vulnerable.

It is interesting that studies on microelements in the blood serum of patients with bronchial asthma showed elevated zinc concentration in female patients, while there was no elevation in male patients. Moreover, there is positive correlation between serum concentration of zinc and serum opsonic activity in both sexes (Urushidate et al., 2010). This suggests intensified work of SOD-way of elimination of ROS, which are produced by neutrophils.

In epithelial cells of respiratory ways zinc ions are concentrated in cytoplasmic vesicles and ciliar basal bodies (Carter et al., 2002). Moreover, zinc is strategically localized in apical cytoplasm of respiratory ways epithelium (AEC), to manage apoptosis linked with activation of caspase-3. At murine model of allergic asthma it was shown (Truong-Tran et al., 2003), that loss of zinc (for example, in the presence of TPEN) AEC is followed by changes in levels of procaspase-3 as well as active caspase-3. There were a more little increasing in levels of only caspases-2 and -6. Activation of caspase-3 in AEC, being treated by TPEN, is readily inhibited by NAC and partly by vitamins C and E. Thus, deficient of zinc in food leads in prospective to increasing of AEC apoptosis.

Probably, a significant flow of zinc inside and through respiratory ways (AE) exists (Zalewski et al., 2005). Most likely, hZIP family of zinc transporters participate in its transfer through plasmatic membranes and immediately after zinc absorption it is packed in cytoplasmic vesicles, which migrate to perinuclear region and apical cytoplasm. Potential source of zinc in AE is its releasing from zinc-rich (due to MT) inflammatory cells. Zinc potentially possesses cytoprotector, secretory, growth-stimulating and signal functions not only for AE,

but also for cells, which interact with this tissue. Increased expression of p53 mRNA takes place in cultures of human epithelial bronchial cells in the medium with decreased zinc concentration (Fanzo et al., 2001).

It is known that zinc in low concentrations forms a bridge between two transmembrane domains of β-2-adrenoreceptor, positively influencing on agonist of binding (Swaminath et al., 2003), which is used as bronchodilator in asthma treatment. Decreasing of zinc concentration in the respiratory ways may increase bronchus spasm, in particular, through influence on muscarinic receptors (Taylor et al., 2000), and preventing activation of activation of acetylcholine receptors, blocking influx of calcium ions. Mast cells, which are key components in allergic as well as in inflammatory processes, are very rich of zinc (Ho et al., 2004). These cells have a well-developed mechanism of zinc absorption and storage in granules due to ZnT4 transporter, which is highly expressed in these cells in humans and animals. Process of degranulation is very sensitive to extracellular zinc (Zalewski et al., 2005).

It is known that T-lymphocytes are more susceptible to zinc deficiency in comparison with B-cells, so T-immune system is more dependent on zinc homeostasis. In particular, it is linked with demand in zinc for secretion of different T-dependent interleukins and cytokines (IL-1, IL-2, IL-4, IFN-γ). The last function of zinc is linked with production of pro-inflammatory cytokines in asthma. In this, T-lymphocytes of СД4+ phenotype are more sensitive to apoptosis than СД8+ (Prasad, 1998). Addition of zinc is able to regulate expression of hZIP1 mRNA in lymphocytes and leucocytes (Andree et al., 2004).

Respiratory ways possess specialized secretory cells (goblet cells), which contain greatly carboxylated glucoseaminoglycans (mucins). It is considered that they may be linked with labile zinc appearance in secretory granules. Aquaporine, potential-dependent proton, chloride channels of ions in respiratory ways and purineergic receptors are subjected to action of zinc (Zsembery et al., 2004).

One of the targets for zinc in mast cells (Aggarwal et al., 2004) is cytoplasmic transcription factor NF-ηh, which is of importance for expression of pro-inflammatory cytokines. Addition of TPEN stimulates translocation of NF-ηh, and inclusion of ionophore, for example, pyrithione, which, on the contrary, increases zinc concentration – blocks the translocation (Zsembery et al., 2004). Reduction of neutrophyls infiltration is an example of anti-inflammatory action of zinc. It is suggested that zinc blocks interaction of leucocyte-associated antigen 1 at neutrophyls and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells of capillaries.

7. RELATIONSHIP OF BIOLOGICAL EFFECTS OF ZINC AND OTHER METALS

Calcium is the first metal for which a role in apoptosis was described. Actually, intracellular concentration of calcium must be maintained at the level enough to activate endonucleases of type I, which are dependent on calcium and magnesium. Increasing of calcium is not essential for early stages of apoptosis, but is necessary to degrade DNA (Torriglia et al., 1997). It is possible to artificially increase intracellular concentration of calcium ions with usage of ionophore (Seve et al., 2002). Among the intracellular mediators of apoptosis, it is zinc that may prevent calcium effects (Lohmann et al., 1993), especially if take into account that zinc gradient on plasmatic membrane is higher than that of calcium (Vogt et al., 2000). Zinc prevents DNA fragmentation in many cell lines during the apoptosis, in particular, by inhibition of activities of Ca- and Mg- dependent endonucleases (Cohen et al., 1984). It is

supposed that this takes place by competitive processes leading to conformational changes in their active centers. However, acting in non-stationary conditions in different directions, Ca and Zn may cause the same effects. For example, calcium activates kinases, but zinc inhibits phosphatases and their final effect is the same – protein phosphorylation (Maret, 2011).

Combined action of Cd-Ca-Zn causes significant inhibition of Zn-stimulated mechanisms of transport (Bergeron et al., 2006). Dose-dependent influence of zinc on uptake Ca and in some cases zinc-induced stimulation of Cd uptake is observed. Cadmium – is one of the most toxic metals, intensively studied during last years, because a number of proteins have the same binding for cadmium as for zinc. Study on consumption of cadmium and zinc at different concentrations of calcium by *Eisenia fetida* (Li et al., 2010) showed, that uptake of zinc does not influence Ca-channel, whereas uptakes of Cd and Zn are pharmacologically different ones. Preliminary treatment with zinc (1.0 μM) does not influence toxic action of cadmium. However, pre-treatment with cadmium changed intracellular distribution of zinc with decrease of membrane-bound zinc and with increase of its content in a cytosole. In the same time, there are data (Brzoska et al., 2001), indicating that zinc at some concentrations has essential influence on uptake, distribution and toxicity of cadmium in the organism. As a whole, increasing of nutritional zinc decreases unfavor effects of cadmium, while its deficiency, on the contrary, increases Cd-toxicity, that may be expressed as Cd-induced testicular pathology with decreased testicular concentrations of Zn and Se, and also their blood serum concentrations the result is decrease in testosterone concentration in the blood plasma and in enzymatic activities of SOD, CAT, Gpx with simultaneous increasing of MDA level. In this case it is perspective to use a combination of Zn and Se in nutrition of Cd-exposed animals that protects the organism from testicular damages and restores antioxidant protective system (Said et al., 2010). In addition selenium and zinc antagonize oxidative stress, apoptosis, and cell cycle changes induced by excess fluoride (Yu et al., 2006).

In C6 rat glioma cells, cadmium caused externalization of phosphatidylserine, breakdown of the mitochondrial membrane potential, activation of caspase-9, internucleosomal DNA fragmentation, chromatin condensation, and nuclear fragmentation (Wätjen et al., 2000). In these conditions Cd-induced DNA fragmentation was independent of inhibition of protein kinase A (PKA), PKC, MAPK, phosphatidylinositol 3-kinase, Ca-calmodulin-dependent protein kinase and protein kinase G. Zinc at concentrations of 10-50 microM protected against apoptosis induced by cadmium, whereas in the presence of TPEN apoptosis increased. With an increasing in extracellular levels of zinc up 150-200 μM in C6 cells only apoptosis observed, which do not depend on the inhibition of PKA, PKC, guanylate cyclase and MAPK, but it was suppressed by the presence of 100 μM lanthanum chloride.

Because zinc and cadmium have a similar chemical coordination, they are simultaneously partners and competitors in binding with MT-s and other proteins. Cadmium is able to replace zinc at zinc-binding sites, causing structural changes there and this leads to incorrect folding and loss of protein activity (Kothinti et al. 2010). Substitution of zinc to cadmium may lead to disruption in signaling pathways (Thehevenod, 2009), impairments in DNA-reparation and gene regulation (Tabatabai et al., 2005).

Copper, zinc and iron – some of the most required metals for different metalloproteins, although their excess may lead to biological damages. Zn, mainly, may by different ways through competitive mechanisms to slow down oxidative mechanisms, induced by Cu and

Fe, including modulation of ROS, maintaining of adequate level of MT-proteins and direct reduction of Cu and Fe amount (Formigary et al., 2007; Santon et al., 2006).
Nanoparticles of copper and zinc express similar toxicity in the organism with its increasing at low pH values (Van Sprang et al., 2001). Addition of EDTA into cultural medium *in vitro* decreases toxic effects of both metals.

In many systems Zn may counteract to catalytic properties of redox-active Fe and Cu from the position of their ability to promote formation UOH by peroxide and superoxide (Powell, 2000). In cells of LEC rats, zinc acetate increased tissue concentration of Zn and MT and decreased concentration of C*и* and Fe due to decreasing of their transport from mucosa to serous intestine walls on the basis of competitive mechanisms (Medici et al., 2002). Competitive inhibition of iron absorption by transporter of bivalent metal in the presence of Zn is observed also in fibroblasts (Santon et al., 2006). It is supposed (Streedhar et al., 2004), that Zn decreases Fe-induced production of hydroxyl radicals, causing increase of GSH and MT levels and supporting stability of sulfhydryl groups. Zn in combination with Fe, in comparison with Fe effects only, decrease significantly apoptotic as well as necrotic index in cell line of fibroblasts (Formigari et al., 2007). In the intestine cells in conditions of ROS-induced signaling system and cell death zinc performed inhibition of apoptosis through decrease of Glu/GO – induced iron uptake and inhibition of Fe-regulating protein 1. This leaded to decrease of intracellular labile iron, reduction of ferritine and expression of MT. Then zinc increased Bcl-2/Bax ratio and decreased activity of caspase-3 (Kilari et al., 2010).

During determination of the degree of toxicity on epithelial cells in rat lungs (by activity of mitochondrial succinate dehydrogenase) the next line V>Zn>Cu>Ni>Fe is obtained (Riley et al., 2003), in that zinc appearance leaded to decrease of negative effect of V and Cu; gave additive effect with Ni, and did not influenced on toxicity of Fe.

Chromium (VI)-induced cytotoxicity and apoptosis are increased in their size in impoverished of zinc cells in chromium (VI) concentrations from 50 to 150 mM (Rudolf et al., 2005). On the contrary, elevated labile zinc was able to protect from apoptosis, induced by 10 mM of chromium (VI). At more high concentration of chromium (50 and 150 mM) a synergic effect is observed, that significantly increases oxidative stress and, correspondingly, apoptosis. It is suggested that it takes place in case of mitochondrial damages. Competitive usage of zinc and chromium (VI) may lead to decrease as well as to increase of ROS levels. Zinc in concentration of 100 mM decreases production of hydrogen peroxide and superoxide-anion during its simultaneous administration with 10 mM of chromium (VI). On the other side, the same concentration of zinc increases level of oxidative stress in cells, if it is administered with 50 and 150 mM of chromium (VI). Thus, effects of zinc deficiency or its increase on Cr(VI)-induced cytotoxicity, oxidative stress, DNA-damages and cell death showed (Rudolf et al., 2005), that 50, 10 and 1μM of Cr(VI) induce cytotoxicity dependent on time and dose in the result of oxidative stress, suppression of antioxidant system and activation of p53-dependent apoptosis. Elevation of intracellular zinc partly decreases Cr(VI)-cytotoxicity, oxidative stress and inhibits Cr(VI)-dependent apoptosis, preventing activation of caspase-3. Decrease of intracellular zinc expands the chromium cytotoxic effect at all tested Cr(VI) concentrations, leading to fast decomposition of cell membranes and nuclear-dispersion features of necrosis.

Compound $Cr(III)(phen)_3$: [(tris (1,10-phenantrolin) chromium(III) chloride)] in action at lymphocytes (Sankaramanivel et al., 2010) is able to provoke apoptogenic changes: decrease level of ATP, increase activity of caspase-3, alter mitochondrial membrane potential, but they are leveled to normal values in case of preliminary treatment of cells by

zinc. In dependence on concentration, $Cr(III)(phen)_3$ induces synthesis of MT-3 isoform, in that function of metal-regulating transcription factor MTF-1 is not inhibited by this compound as it takes place in case of addition of Cr(VI) (Majumder et al., 2003).

N,N`,N``-tris-(2-pyridylmethyl)-cis,cis-1,3,5-triaminocyclohexane; so-named touchpyridin, is a powerful hexadentate chelator of iron and potential agent in combating cancer. It initiates mitochondrial way of cell death, which is p53-independent one. Iron and zinc were (Zhao et al., 2004) main targets for touchpyridine in cells and 9% of total cellular iron and 13% of total cellular zinc were bound by it. Preliminary treatment with any of these metals protected completely cells from cytotoxic action of the preparation.

Effects of other metals on apoptosis in combination with zinc action have not been studied yet (Rana, 2008).

8. ZINC COMPLEX IN CONDITIONS OF IONIZING AND UV IRRADIATION

Study of effects of ionizing as wells as UV-radiation on apoptosis at first is linked with their use in radiotherapy and phototherapy, correspondingly. Understanding of that how to achieve maximum effect in death of cancer cells (it is desirable to protect normal cells) is a critical moment in cancer treatment, and zinc, being active participant of the apoptosis, plays an important role in these processes.

Anticancer effect of Zn-binding compounds may be caused by three different mechanisms (Zheng et al., 2010; Ding et al., 2009). More often complex formation (chelation) is used, when cells are deprived of zinc and dead, mainly, under action of ROS excess. The most known zinc chelator is TPEN (Ding et al., 2008). Another mechanism includes zinc transportation into cells causing apoptosis. Ionophores and shuttles may be acted as transporters (Magda et al., 2008). Ionophores may transport several ions of a metal, so during increase of metal concentration, their cytotoxic effects are increased (for example, ionophore for zinc is, cliochinol (Yu et al., 2009). Shuttles facilitate metal penetration into cell, but their action does not depend on the metal concentration (Lecane et al., 2005).

Ionizing radiation is able to induce in human CNS MT protein as well as expression of MT-2 mRNA. Zinc, inducing synthesis of MT, protects brain tissues from damaging effects of radiation (Zhang et al., 2002). The role of MT, which protects cells form formed free radicals, was considered (Deng et al., 1999) in γ-irradiation (^{60}Co) by doses of 0.5 and 10 Gy. In culture of human cells, CNS and astrocytes, release of lactate dehydrogenase and damage of neuronal dendrites are observed, and preliminary treatment by zinc, inducing induction of MT, served as protection measure. It was shown (Cai et al., 2004), that γ-irradiation in a dose from 15 to 30 Gy causes predominantly apoptosis of astrocytes, but at a dose of 60 Gy (P_γ=0.1 Gy/s) necrotic death of cells prevails. Dose of 30 Gy caused apoptosis increasing in a day, and this effect was significantly decreased by pre-treatment of cells with zinc. Any increasing of MT expression serves as protection from radiation-induced consequences. Role of MT and apoptosis was also studied at thymocytes, in which ionizing radiation causes apoptosis due to formation of peroxides, generated during irradiation or after it. After 2 min. of γ-irradiation (5 Gy, ^{60}Co) of selected by age mice males of MT-1 hyperexpressed (MT-1*) and MT-null transgenic mice, their thymus was removed after 24 hours and basal levels of MT and zinc concentrations were determined. Minimum amount of MT was revealed in MT-null thymus and there was a largest amount of apoptotic cells. Level of peroxides after irradiation was increased by factor of 10-11 (Ramakrishanan et al., 1996) and continued to increase during time. Similar situation was observed in case of lipid peroxidation. Generation

of peroxides and lipid peroxidation of membrane lipids preceded internucleosome fragmentation of DNA as well as morphological changes, characteristic for apoptosis. Treatment of cells by ebselen, which mimics of glutathion peroxidase, sufficiently decreased peroxide levels, providing cells by protection from apoptosis.

Lyposomal Cu/Zn-SOD and Mn-SOD equally decrease radiation-induced fibrosis and provide a possibility to repair normal tissues in the region of stabilized post-radiation fibrosis (Lefaix et al., 1996).

To study relationships between induction of the radiation-induced apoptosis and kinetics of microelements, human leukemic cells were irradiated *in vitro* ^{60}Co, after that character of the cells apoptosis and a pattern of microelements (Fe, Ca, Zn) distribution were evaluated (Harada et al., 2002). It was found that in early stage of apoptosis the maximum level of accumulation was observed for Fe in stromal cell. In the middle-end of the phase accumulation of Fe was decreased, and instead, accumulation of Ca was increased (in decreasing of Zn content) in the nucleus. Authors suggest two stages of apoptosis development: (1) signal from the stromal cell to nuclei of Fe or Fe-containing enzymes and (2) degeneration of nuclei by Ca-dependent enzymes, with releasing of Zn from digested nucleus. These zinc releases may be an additional marker for apoptosis.

8.1 Photodynamic Therapy

Photodynamic therapy (PDT) that is perspective for cancer treatment, includes usage of photosensibilizators in combination with certain wavelength of light irradiation, and this gives an effect of significant increase in production of cytotoxic singlet oxygen as well as other ROS, which cause tumor cells death ROS (Woster, 2006; Casero et al., 2007). Different complexes of zinc are used as photosensibilizators that increases possibility of apoptosis, making:

1. Photosensibilizing effect due to formation of singlet oxygen, which possess strongest cytotoxic effect and
2. Chelators of zinc decrease its available for cells concentration, creating a zinc-deficiency and promoting apoptosis.

Known photosensibilizators are water-soluble conjugates of Zn-protoporphyrin (ZnPP) (Soda et al., 2009; Minguet et al., 2008), and also Zn(II)-phtalocyanine (ZnPc) (Zhou et al., 1996). Their deliverance may be performed by liposomes (Magaraggia et al., 2006), in the presence of cholesterol for stabilization of the system and improvement of photodynamic action (deOliveira et al., 2010). In this localization in Golgi apparatus, photoinactivation gave more than 95% of cell death (5 min. of irradiation in 1 micromole ZnPc), which proceeded by way of parallel development of occasional necrotic and apoptotic processes. Nanoparticles on the basis of chitosan were used for deliverance (Li et al., 2010).

Derivatives of ZnPc, such as octapentyl (ZnOPPc) and octadecyl (ZnODPc*)* (Jori et al., 1998) were tested. Irradiation of tumor region (λ=620-700 nm, 180 mV/cm2, 300 J/cm^2) after 24 h after introduction of photosensibilizator induces significant delay of tumor growth, which was the most long (11 days) for ZnPc and the smallest for (3,5 days) for ZnODPc. Electron microscope study of irradiated tumor samples showed that ZnPc causes early direct damage of malignant cells, mainly through processes, leading to occasional necrotic way, although the restricted contribution of apoptosis was revealed. Importance of apoptosis was increased during usage of ZnOPPc and, especially, ZnODPc.

Effects of cationic phtalocyanins were studied in relation to the blood derivatives. The largest photohemolytic damages were made Zn(II) 2,9,16,23-tetracis [4-(N-methylpyridyloxi)] phtalocyanin (ZnPPc4+) (Spesia et al., 2010).

UV-irradiation was used with simultaneous treatment by cytotoxic preparations (etoposide, camptotecine, melfalan and chlorambucyl), causing fast increasing of intracellular level of hydrogen peroxide, to influence on human promielocytar cells of line HL-60 (Gorman et al., 1997). Pre-treatment of by SOD gave modest protection from UV and did not influence on apoptosis, induced by cytostatics, and catalase could protect cells from them only in their small concentration.

Using TPEN and UV and only UV of keratinocytes (Parat et al., 1997), significant disruptions in stability of DNA and cytoplasmic fragments (mononucleosomes and oligonucleosomes), which characterize cell death by way of apoptosis, were observed. Addition of zinc ions (0.1mM) into cultural medium in both cases prevents processes of disruption of DNA integrity.

Results obtained (Wang et al., 2010) showed complicated and dynamic regulation of UV-induced cell damage, linked with NO-synthase (see Chapter 4).

Treatment of the breast cancer cells by various concentrations of permeable through cell membranes TPEN and membrane non-permeable zinc chelator DTPA resulted to sufficient increasing of cell death due to modulation of intra- and extracellular zinc (Hashemi et al. 2007). Significant increasing of caspases -9 and -3 activity (where expression of caspase-3 is possible), and insufficient increase of caspase-8 activity was observed. Addition of zinc ions prevented DTPA and TPEN mediated cytotoxicity, while addition of calcium or magnesium ions had no effect. Antioxidant NAC inhibited effects of DTPA and TPEN that directs at mediator role of the oxidative stress, which is linked with zinc deficiency. It is interesting that combination of NAC and ions of redox-active copper leads to strong cytotoxic effect at cancer cells, which is not observed in the presence of redox-inactive zinc. Zinc-containing SOD1 and extracellular SOD3 may intensify the process (Zheng et al., 2010), while catalase serves as its inhibitor. This process was named as ROS-generator.

Phtalocyanine derivative, zinc 2,3,9,10,16,17,23,24-octakis[(N,N`-dimethylamino)ethylsulfanyl] phtalocyanine (Rumie-Vittar et al., 2002), demonstrated fine efficiency in phototherapy, leading to apoptosis of human breast cancer cells and adenocarcinoma cells, and 2,9(10), 16(17), 23(24)-tetrakis [(2-trimethylammonium) ethylsulfanyl] phtalocyanine zinc (II) tetraiodide in relation of KB-cells (Marino et al., 2010). The effect depended on concentration of the chelator as well as the light dose and showed apoptosis response with increasing of activity of caspase-3 and splitting of PARP.

Na-Y fluoride nanoparticles were tested as carriers of Zn-phtalocyanine on cancer cells of murine urine bladder. Intracellular accumulation of nanoparticles was not time- and dose-depended. Photosensibilization efficacy of their in activation of Zn-phtalocyanine loaded in their nucleus and membrane with the aim to generate singlet oxygen nanorticles in irradiation with IR-light with λ=980 nm (Guo et al., 2010).

Effects of complexes of zinc with product of condensation of 2-formylpyridine and selen-semicarbazide on matrix metalloproteinases (MMP) MMP-9 and MMP-2 (Bejelogrlic et al., 2010) and cytotoxic activity at eight tumor cells lines in concentration of the agents 1-100 μM and incubation time equal to 48 and 72 hours have been demonstrated. Structure of Zn-

complex had bidentant coordination of the ligand through selen and azomethyn atom of nitrogen. The complex increased MMP-2 activity in supernatants of tested cells. Ni(II)-complex with the same ligand demonstrated opposite effect.

Complexes of zinc with izatin-(H_2L^1) N-methylizatin-3-picolinoil hydrazone (HL^2) (Rodriguez-Arguelles et al., 2004) inhibit DNA synthesis in human leucosis cells and reduction of cells number by ~ 40% in phase S is observed.

Evaluation of cytotoxicity of zinc complex, containing 2,2'-pyridine ligand and Zn $(bpy)_2(NCS)_2$ in relation to neuroblastoma cells and ovarian cancer cells (Shi et al., 2010) showed that the complex either influences a little or does not influence on cell division in the period of their restoration and does not promote DNA cleavage in the presence of ascorbic acid.

A series of Zn-complexes (Raman et al., 2010), which were obtained with use of new type of Schiff bases and demonstrated high antitumor activity and cytotoxicity, were probed.

It is known that zinc chloride is able to inhibit chymotrypsin-like activity of 20S proteasome, however, a complex of zinc with pyrrolidine dithiocarbamate, which suppresses cellular proteasomal activity and proliferation and induces apoptosis in different human cancer (breast and prostate cancer) cell lines is a more powerful factor $(PyDT)_2Zn$ (Milicic et al., 2008). Mechanism of action of the complex does not concern activation of caspases-3, -7 and proceeds through calpaine-dependent mechanism by the way of cleavage of small subunit of calpaine with accumulation of p65 PARP fragment and p36/Bax protein. Moreover, inhibition of proteasome and induction of apoptosis, caused by $(PyDT)_2Zn$, do not blocked by DTT and NAC that implies absence of the way through ROS.

A particular class of supramolecular photosensibilizators is composed of dendrite porphyrines (DP), containing zinc atom inside them. 32(+)DPZn (contains 32 ammonia groups) the largest $^1O_2$-induced cytotoxicity was shown (Nishiyama et al., 2003).

Complexes of zinc with anti-diabetes activity were considered in detail in (Sakurai et al., 2008).

Thus, mechanisms of photosensibilization, mainly, effect by increase of ROS action and accompanying changes in expression of MT-s, however, in the last time, new classes are arisen, which influence on signaling systems by more complicated way.

9. ZINC MAGNETIC ISOTOPE EFFECT IN BIOCHEMISTRY

The magnetic isotope effect was firstly observed in the case of isotope ^{25}Mg in creatine kinase way of ATP synthesis (Buchachenko et al., 2004, 2008), and now it is possible to say about appearance of new direction – spin biochemistry. As for natural isotopes mixture of zinc, there is little more than 4% of magnetic isotope ^{67}Zn (s -5/2). It is known, that rate of enzymatic synthesis of ATP depends on zinc. ATP-producing activity of creatine kinase (CK) and pyruvate kinase (PK), in the presence of $ZnCl_2$, where the zinc atom has a magnetic nucleus ^{67}Zn, was from 2 to 6-fold higher than in the case of non-magnetic zinc (Buchachenko et al., 2010; Orlov et al., 2011). Mitochondria from rat heart muscle demonstrated the similar effect in consideration of ATP yield, produced by CK, as a function of $ZnCl_2$, where the nucleus of zinc was 64 or 67 (*in vitro*). In the first case, (CK) a peak was observed at zinc concentration 5-10 мМ with futher decrease of ATP yield. In the case of PK

and ^{67}Zn at 10 мМ there was plateau, while in the case of ^{64}Zn the shape of the curve was similar to the СК case. These studies allowed suggesting a possibility for particular effects of magnetic isotope of zinc (in comparison with natural pool of isotopes and also with non-magnetic nuclei) on apoptosis of cancer cells that have been registered in our experiments, and the results are under publication.

Mechanism of magnetic isotope effect was suggested by academician Buchachenko A.L. (Buchachenko et al., 2008, 2011) for reaction of phosphorylation and is based on the possibility of singlet-triplet conversion of forming ion-radical pairs and formation of additional triplet channel of ATP synthesis. It is not clear, are other reactions, besides the phosphorylation reaction, subjected to influence of magnetic nuclei of elements. By method of radiation inactivation we have shown earlier (Orlova et al., 2009) that creatine kinase (from *Vipera xanthia*) *in vitro* behaves differently in the presence of magnetic (^{25}Mg) or non-magnetic (^{24}Mg, ^{26}Mg) nuclei of magnesium that indicates presence of conformational component in the "spin" process. However, introduction of ^{67}Zn isotope into ACE, which replaced natural pool of zinc in the active center, does not reveal differences in the enzyme activity *in vitro* regarding peptide substrates in comparison with enzyme containing common zinc (our unpublished results). Seemingly, it is in prospect to see more and more interesting things in this research field.

10. CONCLUSION

Intensive studies of role of zinc in the body demonstrate that its effects encompass the growing number of internal and external pathways, inducing or inhibiting the apoptosis. Possibly, these ways forms a closed cycle, when shift of equilibrium, pH, concentration etc., impairing zinc homeostasis and redistributing it, lead simultaneously to disruption of expression, structure, mutations and disorder a cell rhythm, that is fraught with different diseases and is especially linked with tumor formation. But it is possible to implement blocking of cell proliferation in the same Zn-cycle with the adoption of many stages of mediated solutions to its apoptosis or rehabilitation. The relationship of zinc to transcription factors and signaling pathways looks impressive and makes it possible (though certainly not completely) to understand the involvement of zinc in the proliferation.

However, such an active involvement of zinc grants a hope, that understanding of these "Zn-cycles" may help to make right corrections of native as well as acquired during the life "errors" of the organism.

ACKNOWLEDGEMENTS

This work was supported by RFBR, grant № 10-08-00 680-a.
.

REFERENCES

Abai, H., Haznedaroglu, I.C., Goker, H., Celik, I., Oztli, D., Koray, Z. (2002). Circulating and local bone marrow rennin-angiotensin system in leukemic hamatopoiesis: preliminary evidences. Hematol., 7, 75-82.

Adlard, P.A., Parncutt, J.M., Finkelstein, D.I., Bush, A.I. (2010). Cognitive loss in zinc transporter-3 knock-out mice: a phenocopy for the synaptic and memory deficits of Alzheimer's disease? J. Neurosci., 30, 1631–1636.

Afonso, V., Santos, G., Collin, P., Khatib, A.-M., Mitrovic, D.R., Lomri, N., Leitman, D.C., Lomri, A. (2006). Tumor necrosis factor-α down-regulates human Cu/Zn superoxide dismutase 1 promoter via JNK/AP-1 signalling pathway. Free Radic. Biol. Med., 41, 709-721.

Agay, D., Anderson, R.A., Sandre, C., Bryden, N.A., Alonso, A., Roussel, A.M., Chancerelle, Y. (2005). Alterations of antioxidant trace elements (Zn, Se, Cu) and related metallo-enzymes in plasma and tissues following burn injury in rats. Burns, 31, 366-371.

Aggarwal, B.B., Takada, Y., Shishodia, S., Gutierrez, A.M., Oommen, O.V., Ichikawa, H. (2004). Nuclear transcription factor NfkappaB: role in biology and medicine. Ind. J. Exp. Biol., 42, 341-353.

Aiuchi, T., Mihara, S., Nakaya, M., Masuda, Y., Nakajo, S., Nakaya, K. (1998). Zinc Ions Prevent Processing of Caspase-3 during Apoptosis Induced by Geranylgeraniol in HL-60 Cells. J. Biochem., 124, 300-303

Aksu, S., Beyazit, Y., Haznedaroglu, I.C., Canpinar, H., Kekilli, M., Uner, A. (2006). Over-expression of ACE (CD143) on leukemic blasts as a clue for the activated local bone marrow RAS in AML. Leuk. Lymphoma, 97, 839-844.

Al-Chalabi, A., Hansen, V.K., Simpson, C.L., Xi, J., Hosler, B.A., Powell, J.F., McKenna-Yasek, D., Shaw, C.E., Leigh, P.N., Brown, R.H. (2003) Variants in the ALS2 gene are not assosiated with sporadic ALS. J. Neurogen., 4, 221-222.

Al-Guborya, K.H., Fowlerb, P.A., Garrelc, C. (2010). The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int. J. Biochem. Cell Biol., 42, 1634–1650.

Allen, R.G., Tresini, M. (2000). Oxidative stress and gene regulation. Free Radic. Biol. Med., 28, 463-499.

Amemiya, Y., Azmi, P., Seth, A. (2008). Autoubiquitination of BCA2 RING E3 ligase regulates its own stability and affects cell migration. Mol. Cancer Res., .6, 1385-1396.

An, B., Goldfarb, R.H., Siman, R., Dou, Q.P. (1998). Novel dipeptidyl proteasome inhibitor overcome Bcl-2 protective function and selectively accumulate the cyclin dependent kinase inhibitor p27 and induce apoptosis in transformed, but not normal human fibroblasts. Cell Death Differ, 5, 1062-1075.

Andree, K.B., Kim, J., Kirschke, C.P., Gregg, J.P., Paik, H., Joung, H. (2004). Investigation of lymphocyte gene expression for use as biomarkers for zinc status in humans. J. Nutr., 134, 1716-1723.

Arcenault, J.E., Brown, K.H. (2003). Zinc intake of US preschool children exeeds new dietary reference intakes. Am. J. Clin. Nutr., 78, 1011-1017.

Banci, L., Bertini, I., Ciofi-Baffoni, S., Finney, L.A., Outten, C.E., O'Halloran, T.V. (2002). A new zinc-protein coordination site in intracellular metal trafficking: solution structure of the apo and Zn(II) forms ZntA(46-118). J. Mol. Biol., 323, 883-897.

Banerjee, R., Starkov, A.A., Beal, M.F., Thomas, B. (2009). Mitochondrial dysfunction in the limelight of Parkinson's disease pathogenesis. Biochim. Biophys. Acta, 1792, 651–663.

Barbosa, L.F., Cerqueira, F.M., Macedo, A.F., Garcia, C.C., Angeli, J.P.F., Schumacher, R.I., Sogayar, M.C., Augusto, O., Carrì, M.T., Mascio, P., Medeiros, M.H.G. (2010). Increased SOD1 association with chromatin, DNA damage, p53 activation, and apoptosis in a cellular model of SOD1-linked ALS. Biochim. Biophys. Acta, 1802, 462–471.

Baum, L., Chan, I.H., Cheung, S.K., Goggins, W.B., Mok, V., Lam, L., Leung, V., Hui, E., Ng, C., Woo, J., Chiu, H.F., Zee, B.C. (2010). Serum zinc is decreased in Alzheimer's disease and serum arsenic correlates positively with cognitive ability. Biometals, 23, 173–179.

Beckman, J.S., Estevez, A.G., Crow, J.P., Barbeito, L. (2001). Superoxide dismutase and the death of motoneurons in ALS. Trends Neurosci., 24, S15-S20.

Bejelogrlic, S., Todorovic, T., Bacchi, A., Zec, M., Sladic, D., Srdic-Rajic, T., Radanovic, D., Radulovic, S., Pelizzi, G., Andelkovic, K. (2010). Synthesis, structure and characterization of novel Cd(II) and Zn(II) complexes with the condensation product of 2-formylpyridine and selenosemicarbazide. Antiproliferative activity of the synthezised complexes and related selenosemicarbazone complexes. J. Inorg. Biochem., 104, 673-682.

Belousov, V.V., Fradkov, A.F., Lukyanov, K.A., Staroverov, D.B., Shakhbazov, K.S., Tershikh, A.V., Lukyanov. S. (2006). Genetically encoded fluorescent indicator for intracellular hydrogen peroxide. Nat. Methods., 3, 281-286.

Beltramini, M., Zambenedetti, P., Raso, M., Kayat, M.I., Zatta, P. (2006). The effect of Zn(II) and streptozotocin administration in the mouse brain. Brain Res., 109, 207-218.

Bergeron, P.M., Jumarie, C. (2006) Reciprocal inhibition of Cd2+ and Ca2+ uptake in human intestinal crypt cells for voltage independent Zn-activated pathways. Biochim. Biophys. Acta, 1758, 702-712.

Black, A.T., Joseph, L.B., Casillas, R.P., Heck, D.E., Gerecke, D.R., Sinko, P.J., Laskin, D.L., Laskin, J.D. (2010). Role of MAP kinases in regulating expression of antioxidants and inflammatory mediators in mouse keratinocytes following exposure to the half mustard, 2-chloroethyl ethyl sulfide. Toxicol. Appl. Pharmacol., 245, 352-360.

Blindauer, C.A., Leszczyszyn, O.I. (2010) Metallothioneins: unparalleled diversity in structures and functions for metal ion homeostasis and more. Nat. Prod. Rep., 27, 720-741.

Blindauer, C.A., Harvey, I., Bunyan, K.E., Stewart, A.J., Sleep, D., Harrison, D.J., Berezenko, S., Sadler, P.J. (2009). Structure, Properties, and Engineering of the Major Zinc Binding Site on Human Albumin. J. Biol. Chem. 284, 23116-23124.

Blindauer, C.A., Schmid, R. (2010). Cytosolic metal handling in plants: determinants for zinc specificity in metal transporters and metallothioneins. Metallomics, 2, 510-529.

Bomar, M.G., Souza, S.D., Bienko, M., Dikic, I., Walker, G.C., Zhou, P. (2010). Unconventional Ubiquitin Recognition by the Ubiquitin-Binding Motif within the Y Family DNA Polymerases i and Rev1. Mol. Cell, 37, 408–417.

Boulon, S., Westman, B.J., Hutten, S., Boisvert, F.M., Lamond, A.I. (2010). The Nucleolus under Stress. Mol. Cell, 40, 216-226.

Bowling, A.C., Barkowski, E.E., McKenna-Yasek, D. (1995). Superoxide dismutase concentration and activity in familian amyotrophic lateral sclerosis. J. Neurochem., 64, 2366-2369.

Brahemi, G., Kona, F.R., Fiasella, A., Buac, D., Soukupov, J., Brancale, A., Burger, A.M., Westwell, A.D. (2010). Exploring the structural requirements for inhibition of the ubiquitin E3 ligase breast cancer associated protein 2 (BCA2) as a treatment for breast cance. J. Med. Chem., 53, 2757–2765.

Brenner, C., Kroemer, G. (2000). Apoptosis. Mitocgondria – the death signal integrators. Science, 18, 1150-1151.

Brown, G.C., Borutaite, V. (2008). Regulation of apoptosis by the redox state of cytochrome C. Biochim. Biophys. Acta, 1777, 877-881.

Brunelle, J.K., Letai, A. (2009) Control of mitochondrial apoptosis by the Bcl-2 family. J. Cell Sci., 122, 437-441.

Burdette, C.J., Lippard, S.J. (2003). Meeting of the minds: metalloneurochemistry. Proc. Natl. Acad. Sci. USA, 100, 3605-3610.

Burger, A.M., Seth, A. (2005). The ubiquitin-mediated protein degradation pathway in cancer: therapeutic implications. Eur. J. Cancer, 40, 2217-2229.

Burger, A.M., Gao, Y.G. Amemiya, Y., Kahn, H.J., Kitching, R., Yang, Y.L., Sun, P., Narod, S.A., Hanna, W.M., Seth, A.K. (2005). A novel RING-type ubiquitin ligase breast cancer-associated gene 2 correlates with outcome in invasive breast cancer. Cancer Res., 65, 10401-10412.

Brzoska, M.M., Moniuszko-Jakoniuk, J. (2001). Interaction between Cd and Zn in the organism. Food Chem. Toxicol. 39, 967-980.

Buchachenko, A.L., Kuznetsov, D.A., Shishkov, A.A. (2004). Spin Biochemistry: magnetic isotope effect in the reaction of creatine kinase with methylmercury chloride. J. Phys. Chem. A, 108, 707-710.

Buchachenko, A.L., Kuznetsov, D.A., Breslavskaya, N.N., Orlova, M.A. (2008). Magnesium isotope effect in enzymatic phosphorylation. J. Phys. Chem. B, 112, 2548-2556.

Buchachenko, A.L., Chekhonin, V.P., Orlov, A.P., Kuznetsov, D.A. (2010). Zinc-related magnetic isotope effect in the enzymatic ATP synthesis: a medicinal potential of the nuclear spin selectivity phenomena., Int. J. Mol. Med. Adv. Sci, 6, 34-37.

Buchachenko, A.L., Breslavskaya, N.N., Chekhonin, V.P., Orlov, A.P., Arkhangelsky, S.E., Kuznetsov, D.A. (2011). Phosphate transfer enzymes as the nuclear spin selective nanoreactors. Int. Res. J. Pure Applied Chem., 1, 1-15.

Cai, L., Iskander, S., Cherian, G., Hammond, R.R. (2004). Zinc or cadmium-pre-induced metallothionein protect human central nervous system cells and astrocytes from radiation-induced apoptosis. Toxicol. Lett., 146, 217-226.

Carter, J.E., Truong-Tran, A.Q., Glosser, D., Ho, L., Ruffin, R.E., Zalewski, P.D. (2002) Involvement of redox events in caspase activation in Zn-depleted airway epithelium cells. Biochem . Biophys. Res. Commun., 297, 1062-1070.

Casero, R.A., Marton, L.J. (2007). Targeting polyamine metabolism and function in cancer and other hyperproliferative diseases. Nature Rev. Drug Discovery, 6, 373-390.

Ciechanover, A. (1998) The ubiquitin-proteasome pathway: on protein death and cell life. EMBO J., 17, 7151-7160.

Cioni, P., Pesce, A., Morozzo della Rocca B., Castelli, S., Falconi, M., Parrilli, L., Bolognesi, M., Strambini, G., Desideri, A. (2003). Active-site copper and zinc ions modulate the quaternary structure of prokaryotic Cu,Zn-superoxide dismutase. J. Mol. Biol., 326, 1351-1360.

Chandra, D., Bratton, S.B., Person, M.D., Tian, Y., Martin, A.G., Fearnhead, H.O., Gandhi, V., Tang, D.G. (2006). Intercellular nucleotides act as critical prosurvival factors by binding to cytochrome C and inhibiting apoptosome. Cell, 125, 1333-1346.

Chakraborti, S., Bahnson, B.J. (2010) Crystal structure of human senescence marker protein 30: Insights linking structural, enzymatic, and physiological functions. Biochemistry, 49, 3436-3444.

Chang, K.-L., Hung, T.-C., Hsieh, B.-S., Chen, Y., Chen, T.F., Cheng, H.L. (2006). Zinc at pharmacologic concentrations affects cytokine expression and induced apoptosis of human peripheral blood mononuclear cells. Nutr., 22, 465-474.

Chao, B., Kerr, D.A., Cheng, E., Hardwick, J.M. (2000). Aven, a novel inhibitor of caspase activation binds Bcl-xl and Apaf-1. Mol. Cell, 6, 31-40.

Chao, Y., Fu, D. (2004). Kinetic study of the antiport mechanism of an *E. coli* zinc transporter ZntB. J. Biol. Chem., 279, 12043-12047.

Chimienti, F., Seve, M., Richard, S., Mathieu, J., Favier, A. (2001). Role of cellular zinc in programmed cell death: temporal relationship between zinc depletion, activation of caspases and cleavage of Sp family transcription factors. Biochem. Pharmacol., 62, 51-62.

Chipuk, J.E., Green, D.R. (2008). How do BCL-2 proteins induce mitochondrial outer membrane permeabilization? Trends Cell Biol., 18, 157–164.

Cleement, M.V., Ponton, A., Pervaiz, S. (1998). Apoptosis induced by hydrogen peroxide is mediated by decreased superoxide anion concentration and reduction of intracellular milieu. FEBS Lett., 440, 13-18.

Cleveland, D.W. (1999). From charcot to SOD1: mechanisms of selective motor neuron death in ALS. Neuron, 24, 515-520.

Cohen, J.J., Duke, R.C. (1984). Glucocorticoid activation of calcium-dependent endonuclease in thymocyte nuclei leads to cell death. J. Immunol., 132, 38-42.

Colvin, R.A., Davis, N., Nipper, R.W., Carter, P.A. (2000). Zinc transport in the brain routes of zinc influx and efflux in neurons. J. Nutr., 130 (Suppl.), 1484S-1487S.

Colvin, R.A., Holmes, W.R., Fontainea, C.P., Maret, W. (2010). Cytosolic zinc buffering and muffling: Their role in intracellular zinc homeostasis. Metallomics, 2, 306-315.

Corvol, P., Eyries, M., Soubrier, F. (2004). Peptidyl-dipeptidase A/Angiotensin I-converting enzyme. In: Handbook of Proteolytic Enzymes. Ed. A.A. Barret, N.D. Rawlings, J.F. Woessner, Elsevier Acad. Press, N.Y., pp. 332-349.

Coyle, P., Philcox, J.C., Carey, L.C., Rofe, A.M. (2002). Metallothionein the multipurpose protein. Cell Mol. Life Sci., 59, 627-647.

St.Croix, C.M., Wasserloos, K.J., Dineley, K.E., Reynolds, I.J., Levitan, E.S., Pitt, B.R. (2002). Nitric oxide induced changes in intracellular zinc homeostasis are mediated by metallothionein/thionein. Am. J. Physiol. Lung Cell Mol. Physiol., 282, L185-L192.

Cuajungco, M.P., Lees, G.J. (1997) Zinc and Alzheimer`s disease: is there a direct link. Brain Res. Rev., 23, 219-236.

Cui, L., Takagi, Y., Wasa, M., Sando, K., Khan, J., Okada, A. (1999) Nitric oxide synthase inhibitor attenuates intestinal damage induced by zinc deficiency in rats. J. Nutr., 129, 792-798.

Curtin, J.F., Donovan, M., Cotter, T.G. (2002). Regulation and measurement of oxidative stress in apoptosis. J. Immunol. Meth., 265, 49– 72.

Damiano, M., Starkov, A.A., Petri, S., Kipiani, K., Kiaei, M., Mattiazzi, M. (2006). Neural mitochondrial Ca2+ capacity impairment precedes the onset of motor symptoms in G93A Cu/Zn-superoxide dismutase mutant mice. J. Neurochem., 96, 1349–1361.

Danielson, K., Ohi, S., Huang, P. (1982) Immunochemical detection of metallothionein in specific epithelial cells of rat organs. Proc. Nat. Acad. Sci. USA., 79, 2301-2304.

Davis, D.A., Newcomb, F.M., Starke, D.W., Ott, D.E., Mieyal, J.J., Yarchoan, R. (1997). Reversible oxidation of HIV-2 protease. J. Biol. Chem., 272, 25935-25940.

Decaria, L., Bertini, I., Williams, R.J.P. (2010). Zinc proteomes, phylogenetics and evolution. Metallomics, 2, 706–709.

Defenini, L., Zimmerman, E.A., Weare, J.A., Alhenc-Gelas, F., Erdos, E.G. (1983). Angiotensin-converting enzyme in epithelial and neuroepithelial cells. Neuroendocrinol., 37, 32-40.

Deng, D.X., Cai, L., Chakrabarti, S., Cherian, M.G. (1999). Increased radiation-induced apoptosis in mouse thymus in the absence of metallothionein. Toxicol., 134, 39-49.

Ding, W.Q., Yu, H.J., Lind, S.E. (2008). Zinc-binding compounds induce cancer cell death via distinct modes of action. Cancer Lett., 271, 251–259.

Ding, W.Q., Lind, S.E. (2009). Metal ionophores – an emerging class of anticancer drugs. IUBMB Life, 61, 1013–1018.

Donadelli, M., Pozza, E.D., Scupoli, M.T., Costanzo, C., Scarpa, A., Palmieri, M. (2009). Intracellular zinc increase inhibits p53 pancreatic adenocarcinoma cell growth by ROS/AIF-mediated apoptosis. Biochim. Biophys. Acta, 1793, 273-280.

Dreosti, I.E. (1993). Recommended dietary intakes of iron, zinc and other inorganic nutrients and their chemical form and bioavailability. Nutr., 9, 542-545.

Dua, H., Yana, Sh.S. (2010). Mitochondrial medicine for neurodegenerative diseases. Int. J. Biochem. Cell Biol., 42, 560–572.

Duce, J.A., Bus, A.I. (2010). Biological metals and Alzheimer's disease: Implications for therapeutics and diagnostics. Progr. Neurobiol., 92, 1-18.

Duffy, J.Y., Overmann, G.L., Keen, C.L., Clegg, M.S., Daston, G.P. (2004). Cardiac abnormalities induced by zinc deficiency are assosiated with atterations in the expression of genes regulated by the zinc-finger transcription factor GATA-4. Birth Defects Res. B Dey Reprod. Toxicol., 71, 102-109.

Dumay, A., Rincheval, V., Trotot, P., Mignotte, B., Vayssiere, J.L. (2006). The superoxide dismutase inhibitor diethyldithiocarbamate has antagonistic effects on apoptosis by triggering both cytochrome C release and caspase inhibition. Free Radic. Biol. Med., 40, 1377-1390.

Ehlers, M.R.W., Riordan, J.F. (1989). Angiotensin-converting enzyme: new concepts concerning its biological role. Biochemistry, 28, 5311-5318.

Elchuri, S., Oberley, T.D., Qi, W., Eisenstein, R.S., Roberts, L.J., Van Remmen, H. (2005). Cu/Zn SOD deficiency leads to persistent and widespread oxidative damage and hepatocarcinogenesis later in life. Oncogene., 24, 367-380.

Emerit, J., Samuel, D., Pavio, N. (2005). Cu/Zn-superoxide dismutase as a potential antifibrotic drug for hepatitis C related fibrosis. Biomed. Pharmacotherapy., 60, 1-4.

Estevez, A.G., Crow, J.P., Sampson, J.B., Reiter, C., Zhuang, Y., Richardson, G.J. (1999) Induction of nitric oxide-dependent apoptosis in motor neurons by zinc-deficient superoxide dismutase. Science, 286, 2498-2500.

Fadeel, B., Ottosson, A., Pervaiz, S. (2008). Big wheel keeps on turning: apoptosome regulation and its role in chemoresistance. Cell Death Differ, 15, 443-452.

Faiz, M., Acarin, L., Peluffo, H., Villapol, S., Castellano, B., Gonzalez, B. (2006). Antioxidant Cu/Zn SOD: expression in postnatal brain progenitor cells. Neurosci. Lett., 401, 71–77.

Faller, P., Hureau, C. (2009). Bioinorganic chemistry of copper and zinc ions coordinated to amyloid-β peptide. Dalton Trans., 1080–1094. Doi: 10.1039/b813398.

Fanzo, J.C., Reaves, S.K., Cui, L., Zhu, L., Wu, J.Y., Wang, J.R. (2001). Zinc status affects p53, gadd45 and c-fos expression and caspase-3 activity in human bronchial epithelian cells. Am. J. Physiol. Cell Physiol., 281, C751-C757.

Farnebo, M., Bykov, V., Wiman, K. (2010). The p53 tumor suppressor: A master regulator of diverse cellular processes and therapeutic target in cancer. Biochem. Biophys. Res. Commun., 396, 85–89.

Faust, K., Gehrke, S., Yang, Y., Yang, L., Beal, F., Lu, B. (2009). Neuroprotective effects of compounds with antioxidant and anti-inflammatory properties in a Drosophila model of Parkinson's disease. BMC Neurosci., 10, 109-111.

Feng, P., Li, T.L., Guan, Z.X. (2002). Direct effect of zinc on mitochondrial apoptogenesis in prostate cells. Prostate, 52, 311-318.

Ferguson, H.A., Marietta, P.M., VanDenBerg, C.L. (2003). UV-induced apoptosis is mediated independent of caspase-9 in MCF-7 ceels: a model for cytochrome C resistance. J. Biol. Chem., 278, 45793-45804.

Filchenkov, A.A., Zavelevich, M.P., Butenko, Z.A. (2001). Induction of apoptosis in human malignant lymphoid cells by DNA-damaging agents with different mechanisms of action. Exp. oncol. (Russ.), 23, 170-174.

Filchenkov, A.A. (2009). The involvement of the Fas/Fas-ligand system in the regulation of homeostasis and function of immune cells. Allergol. Immunol. (Russ.), 10, 37-40.

Fleisher, T.A. (1997). Apoptosis. Ann. Aller. Asth. Immnol., 78, 245-250.

Formigari, A., Irato, P., Santon, A. (2007). Zinc, antioxidant system and metallothionein in metal mediated-apoptosis. Compar. Biochem. Physiol. (C), 146, 443-459.

Fraker, P.J., Telford, W.G. (1997). A reappraisal of the role of zinc in life and death decisions of cells. Proc. Soc. Exp. Biol. Med., 215, 229-236.

Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., DeLuca, M., DeBenedictis, E. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N.Y. Acad. Sci., 908, 244-247.

Franklin, R.B., Mai, J., Zou, J., Guan, Z., Kukoyi, B.J., Feng, P. (2003). Human ZIP1 is a major zinc uptake transporter for the accumulation of zinc in prostate cells. J. Inorg. Biochem., 96, 435-442.

Frazzini, V., Rockabrand, E., Mocchegiani, E., Sensi, S.L. (2006). Oxidative stress and brain aging: is zinc the link? Biogerontol., 7, 307-314.

Frederikson, C.J., Suh, S.W., Silva, D., Thompson, R.B. (2000). Importance of zinc in the central nervous system: the zinc containing neuron. J. Nutr., 130(Suppl.), 14715-14835.

Frederickson, C.J., Cuajungco, M.P., LaBuda, Suh, S.W. (2002). Nitric oxide causes apparent of zinc from presynaptic boutons. Neurosci., 115, 471-474.

Frederickson, C.J. (2003) Imaging zinc: old and new tools. Sci. STKE, 182, 18-19.

Frederickson, C.J., Koh, J.Y., Bush, A.I. (2005). The neurobiology of zinc in health and disease. Nat. Rev. Neurosci., 6, 449-455.

Friedlich, A.L., Lee, J.Y., van Groen, T., Cherny, R.A., Volitakis, I., Cole, T.B., Palmiter, R.D., Koh, J.Y., Bush, A.I. (2004). Neuronal zinc exchange with the blood vessel wall promotes cerebral amyloid angiopathy. J. Neurosci., 24, 3453–3459.

Frohlich, K.U., Madeo, F. (2001). Apoptosis in yest: a new model for aging research. Exp. Gerontol., 37, 27-31.

Fulda, S., Gorman, A.M., Hori, O., Samali, A. (2010). Cellular stress responses: cell survival and cell death. Int. J. Cell Biol., 214-274.

Fumagalli, S., DiCara, A., Neb-Gulati, A., Natt, F., Schwemberger, S., Hall, J., Babcock, G.F., Bernardi, R., Pandolfi, P.P., Thomas, G. (2009). Absence of nucleolar disruption after impairment of 40S ribosome biogenesis reveals an rpL11-translation-dependent mechanism of p53 induction. Nat. Cell Biol., 11, 501–508.

Gans, B., Jheon, A. (2004). Zinc finger transcription factors in skeletal development. Crit. Rev. Oral Biol. Med., 15, 282-297.

Gao, X., Talalay, P. (2004). Induction of phase2 genes by sulforaphane protect retinal pigment epithelial from photooxidative damage. Proc. Natl. Acad. Sci. USA, 101, 10445-10451.

Garrett, S.H., Sens, M.A., Shukla, D., Nestor, S., Somji, S., Todd, J.H., Sens, D.A. (1999). Metallothionein isoform-3 expression in the human prostate and cancer-derived cell lines. Prostate, 41, 196-202.

Garrett, S.H., Sens, M.A., Somji, S., Todd, J.H. (1999). Expression of MT-3 protein in the human kidney. Toxicol., 105, 207-221.

Gerbaud, P., Petzold, L., Ther'rond, P., Anderson, W.B., Evain-Brion, D., Raynaud, F. (2005). Differential regulation of Cu, Zn- and Mn-superoxide dismutases by retinoic acid in normal and psoriatic human fibroblasts. J. Autoimmun., 24, 69-78.

Giacconi, R., Cipriano, C., Muzzioli, M., Gasparini, N., Orlando, F., Mocchegiani, E. (2003). Interralationships among brain, endocrine and immune response in aging and succeseful aging role of metallothionein III isiform. Mech. Aging Dev., 124, 371-378.

Giansanti, V., Dona, F., Tillhon, M., Scovassi, A.I. (2010). PARP inhibitors: New tools to protect from inflammation. Biochem. Pharmacol., 80, 1869-1877

Gomez-Sarosi, L.A., Strasberg-Rieber, M., Rieber, M. (2010). H_2O_2 preferentially synergizes with nitroprusside to induce apoptosis associated with superoxide dismutase dysregulation in human melanoma irrespective of p53 status: Antagonism by o-phenanthroline. Chem. Biol. Inter., 188, 134–143.

Gorman, A., McGowan, A., Cotter, T.G. (1997). Role of peroxide and superoxide anion during tumour cell apoptosis. FEBS Lett., 404, 27-33.

Green, D.R. (2005). Apoptotic pathways: ten minutes to death. Cell, 121, 671-674.
Green, D.R., Kroemer, G. (2009). Cytoplasmic functions of the tumour suppressor p53. Nature, 458, 1127–1130.
Grider, A., Mouat, M.F., Scrimgeour, A.G. (2007). Consumption of moderately Zn- deficient and Zn-supplemented diet affects soluble protein expression in rat soleus muscle. J. Nutr. Biochem., 18, 753-759.
Grigoriev, M.Ju, Imyanitov, E.N., Hunson, K.P. (2003). Apoptosis in standart and pathology. Med. Acad. J. (Russ.), 3, 3-11.
Gromova, O., Sotnikova, N.Yu, Kataev, S.I., Galustyan, A.N., Krasnykh, L.M., Mazina S.B. (2005). The protective role of cerebrolysin-induced gene expression metallothionein-I and metallothionein-II in cerebral focal ischemia in rats. Cytokins and inflammation (Russ.), 4, 42-46.
Guo, H., Qian, H., Idris, N.M., Zhang, Y. (2010). Singlet oxygen-induced apoptosis of cancer cells using upconversion fluorescent nanoparticles as a carrier of photosensitizer. Nanomed.: Nanotechnol. Biol. Med., 6, 486-495.
Hajnal, A. (2002). Fine-time the RAS signalling pathway: Zn^{2+} makes the difference. Mol. Cell., 9, 927-928.
Hakue, M.E., Asanuma, M., Higashi, Y., Miyazaki, I., Tanaka, K., Ogawa, N. (2003). Overexpression of Cu,Zn-superoxide dismutase protect neuroblastoma cells against dopamine cytotoxicity accompanied by increase in their glutathione level. Neurosci. Res., 47, 31-37.
Hamatake, M., Iguchi, K., Hirano, K., Ishida, R. (2000). Zinc induces mixed types of celldeath, necrosis and apoptosis, in molt-4 cells. J. Biochem. (Tokyo), 128, 933-939.
Hancock, J.T., Desikan, R., Neill, S.J. (2001). Does the redox status of cytochrome C act a fail-safe mechanism in the regulation of programmed cell death? Free Radic. Biol. Med., 31, 697-703.
Hand, C.K., Devon, R.S., Gros-Louis, F., Rochefort, D., Khoris, J., Meininger, V., Bouchard, J.P., Camu, W., Hayden, M.R., Rouleau, G.A. (2003). Mutation screening of the ALS2 gene in sporadic and familial ALS. Arch. Neurol., 60, 1768-1771.
Harada, S., Tamakawa, Y., Ishii, K., Tanaka, A., Saton, T., Matsuyama, S., Yamazaki, H., Kamiya, T., Sakai, T., Arakawa, K., Saiton, M., Oikawa, S., Sera, K. (2002). The kinrtics of Fe and Ca for the development of radiation-induced apoptosis by micro-PIXE imaging. Nucl. Instr. Meth. Phys. Res., B, 189, 437-442.
Hashemi, M., Ghavami, S., Eshraghi, M., Booy, E.P., Los, M. (2007). Cytotoxic effects of intra and extracellular zinc chelation on human breast cancer cells. Eur. J. Pharmacol., 557, 9-19.
Hashimoto, M., Rockenstein, E., Crews, L., Maslian, E. (2003). Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer`s and Parkinson`s diseases. Neuromol. Med., 4, 21-36.
Harnedaroglu, I.C., Arici, M., Buyukasik, Y. (2000). A unifying hypothesis for the rennin-angiotensin system and hematopoiesis: sticking the pieces together with the JAC-STAT pathway. Med. Hypotheses., 54, 80-83.
Haznedaroglu, I.C., Ozturk, M.A. (2003). Towards the understanding of the local hemapoietic bone marrow rennin-angiotensin system. Int. J. Biochem. Cell Biol., 35, 867-880.
He, C., Klionsky, D.J. (2009). Regulation mechanisms and signaling pathways of autophagy. Annu. Rev. Genet., 43, 67–93.
Henning, B., Meerarani, P., Ramadass, P., Toborek, M., Malecki, A., Slim, R. (1999). Zinc nutrition and apoptosis of vascular endothelial cells implications in atherosclerosis. Nutrition, 10, 744-748.

Hershko, A., Ciechanover, A. (1998). The ubiquitin system. Annu. Rev. Biochem., 67, 425-479.

Hidalgo, M.C., Exposito, A., Palma, J.M., Higuera, M. (2002). Oxidative stress generated dietary Zn-deficiency: studies in rainbow trout (Oncorhynchus mykiss). Int. J. Biochem. Cell Biol., 34, 183-193.

Hindle, A.G., Lawler, J.M., Campbell, K.L., Horning, M. (2010). Muscle aging and oxidative stress in wild-caught shrews. Compar. Biochem. Physiol. B., 155, 427–434.

Ho, L.H., Ratnaike, R.N., Zalewski, P.D. (2000). Involvement of intracellular labile zinc in suppression of DEVD-caspase activity in human neuroblastoma cells. Biochem. Biophys. Res. Commun., 268, 148-154.

Ho, L.H., Ruffin, R.E., Murgia, C., Li, L., Krilis, S.A., Zalewski, P.D. (2004). Label zinc and zinc transporter ZnT4 in mast cell granules role in regulation of caspase activation and NF-kB translocation. J. Immunol., 172, 7750-7760.

Huang, J., Klionsky, D.J. (2007) Autophagy and disease. Cell Cycle, 6, 1837-1849.

Huang, L., Gitschier, J. (1997). A novel gene involved in zinc transporter is deficient in the lethal milk mouse. Nat. Genet., 17, 292-297.

Huang, L., Kirschke, C.P., Gitschier, J. (2002). Functional characterization of a novel mammalian zinc transporter, ZnT6. J. Biol. Chem., 277, 26389-26395.

Igbal, K., Alonso, A.C., Chen, S., et al. (2005). Tau pathology in Alzheimer disease and other taupathies. Biochim. Biophys. Acta, 1739, 198-210.

De la Iglesia, S., Lypez-Jorge, C.E., Gymez-Casares, M.T., Castellano, A.L., Cabrera, P.M., Brito, J.L., Cabrera, A.S., Labarta, T.M. (2009). Induction of apoptosis in leukemic cell lines treated with captopril, trandolapril and losartan: A new role in the treatment of leukaemia for these agents. Leuk. Res., 33, 810–816.

De la Iglesia, S., Gomez-Casares, M.T., Lopez-Jorge, C.E., Gonzalez-Leiza, S.M., et al. (2006). Reievance of renin expression by real-time PCR in acute myeloid leukemia. Leuk. Lymphoma, 47, 409-416.

Iitaka, M., Kakinuma, S., Fujimaki, S., Oosuga, I., Fujita, T., Yamanaka, K., Wada, S., Katayama, S. (2001). Induction of apoptosis and necrosis by zinc in human thyroid cancer cell lines. J. Endocrinol., 169, 417–424.

L.I.Ivanov, N.D.Ukhterova, E.I.Geranushkina (2008). Features of the immune status of zinc and copper homeostasis in chronic obstructive pulmonary disease in a geochemically due to zinc deficiency. Healthcare Chuvashia (Russ.), №2, 39-45.

Ivanova, O.M. (2008). The importance of α-macroglobuline for pathogenesis of coronary artery disease. Bull. New Med. Technol. (Russ.), 15, 109-112.

Jacob, C., Maret, W., Vallee, B.L. (1998). Control of zinc transfer between thionein, metallothionein and zinc proteins. Proc. Natl. Acad. Sci. USA, 95, 3489-3494.

Jankowski-Henning, M.A., Clogg, M.S., Daston, G.P., Rogers, J.M., Keen, C.L. (2000). Zn-deficient rat embryos have increased caspase-3-like activity and apoptosis. Biochem. Biophys. Res. Comm, 271, 250-256.

Jensen, K.P., Rykaer, M. (2010). The building blocks of metallothioneins: heterometallic Zn^{2+} and Cd^{2+} clusters from first-principles calculations. Dalton Trans., 39, 9684–9695.

Jiang, J., Serinkan, B.F., Tyurina, Y.Y., Borisenko, G.G., Mi, Z., Robbins, P.D., Schroit, A.J., Kagan, V.E. (2003). Peroxidation and externalization of phosphatidylserine associated with release of cytochrome C from mitochondria, Free Radic. Biol. Med., 35, 814-825.

Jiang, W., Shen, T., Han, Y, Pan, Q., Liu, C. (2006). Divalent-metal-dependent nucleolytic activity of Cu,Zn-superoxide dismutase. J. Biol. Inorg. Chem., 11, 835–848.

Jiang, W., Han, Y., Pan, Q., Shen, T., Liu, C. (2007). Roles of exogenous divalent metals in the nucleolytic activity of C/Zn-superoxide dismutase. J. Inorg. Biochem., 101, 667-677.

Jori, G., Fabris, C. (1998). Relative contributions of apoptosis and random necrosis in tumour response to photodynamic therapy: effect of the chemical structure of Zn(II)-phthalocyanines. J. Photochem. Photobiol. (Biol.), 43, 181-185.

Jung, T., Catalgol, B., Grune, T. (2009). The proteasomal system. Mol. Asp. Med., 30, 191–296.

Kabashi, E., Valdmanis, P.N., Dion, P., Rouleau G.A. (2007). Oxidized misfolded superoxide dismutase-1 the cause of all ALS? Ann. Neurol., 62, 553-559.

Kabe, T., Yamaguchi-Iwai, Y., Sasaki, R., Nagao, M. (2004). Overview of mammalian zinc transporter. Cell Mol. Life Sci., 61, 49-68.

Kagan, V.E., Borisenko, G.G., Tyurina, Y.Y., Tyurin, V.A., Jiang, J., Potapovich, A.I., Kini, V., Amoscato, A.A., Fujii, Y. (2004). Oxidative lipidomics of apoptosis redox catalytic interactions of cytochrome C with cardiolipin and phosphatidylserine. Free Radic .Biol. Med., 37, 1963-1985.

Kalinina, E.V., Chernov, N.N., Saprin, A.N. (2008). Thio-, peroxi- and glutareduxines in cellular redox-dependent processes. Adv. Biol. Sci. (Russ.), 48, 319-358.

Kanasaki, K., Koya, D., Sugimoto, T., Isono, H., Kashiwagi, A., Haneda, M. (2003). N-Acetyl-seryl-aspartyl-lysyl-proline inhibits TGF-beta-mediated plasminogen activator inhibitor-1 expression via inhibition of Smad pathway in human mesangial cells. Am. Soc. Nephrol., 14, 863-872.

Kang, Y.J., Zhou, Z. (2005). Zinc prevention and treatment of alcohol liver disease. Mol. Aspects Med., 26, 391-404.

Karsakova, L.M., Ukhterova, N.D., Borisova, L.B., Ivanov, L.I. (2008). Immunological and immunogenetic markers of chronic obstructive pulmonary disease for natural zinc deficiency. Med. Immunol. (Russ.), №6, 513-518.

Kilari, S., Pullakhandam, R., Nair, K.M. (2010). Zinc inhibits oxidative stress-induced iron signaling and apoptosis in Caco-2 cells. Free Radic. Biol. Med., 48, 961-968.

Kim, B.J., Kim, Y.H., Kim, S., Kim, J.W., Koh, J.Y., Oh, S.H., Lee, M.K., Kim, K.W., Lee, M.S. (2000). Zinc as a paracrine effector islet cell death. Diabetes, 49, 367-371.

Kim, E.K., Choi, E.J. (2010). Pathological roles of MAPK signaling pathways in human diseases. Biochim. Biophys. Acta, 1802, 396-405.

Kim, H.E., Du, F., Fang, M., Wang, X. (2005). Formation of apoptosome is initiated by cytochrome C-induced dATP hydrolysis and subsequent nucleotide exchange on Araf-1. Proc. Natl. Acad. Sci. USA, 102, 17545-17550.

Komura, H., Minakami, H., Otsuki, K., Shoji, A. (2000). Cu,Zn-superoxide dismutase inhibits lactate dehydrogenase release and protect against cell death in murine fibroblasts pretreated with UV-radiation. Cell Biol., 24, 459-465.

Kondoh, G., Tojo, H., Komazawa, N., Murata, C., Yamagata, K., Maedam Y. (2005). Angiotensin-converting enzyme is GPI-anchored protein releasing factor crucial for fertilization. Nat. Med., 11, 160-166.

Kondoh, G., Watanabe, H., Tashima, Y., Maeda, Y., Kinoshita, T. (2008). Testicular angiotensin-converting enzyme with different glycan modification: characterization on glycosylphosphatidylinositol-anchored protein releasing and dipeptidase activity. J. Biochem., 145, 115-133.

Korichneva, I., Hoyos, B., Chua, R., Levi, E., Hammerling, U. (2002). Zinc release from protein kinase C as the common event during activation by lipid second messenger or reactive oxygen. J. Biol. Chem., 277, 7–31.

Koriyama, H., Kouchi, Z., Umeda, T., Saido, T.C., Momoi, T., Ishiura, S., Suzuki, K. (1999). Proteolytic activity of protein kinase C ε and δ by caspase-3 in U937 cells during chemotherapeutic agent-induce apoptosis. Cell Signal., 11, 831-838.

Kothinti, R., Blodgett, A., Tabatabai, N.M., Petering, D.H. (2010). Zn-finger transcription factor Zn3-Sp1 reactions with Cd^{2+}. Chem. Res. Toxicol., 23, 405–412.

Kozlowski, H., Janicka-Klos, A., Brasun, J., Gaggelli, E., Valensin, D., Valensin, G. (2009). Copper, Iron and zinc ions homeostasis and their role in neurodegenerative disorders (metal uptake, transport, distribution and regulation). Coord. Chem. Rev., 253, 2665-2685.

Krasowska, A., Włostowski, T., Bonda, E. (2004). Zinc protection from fluoride-induced testicular injury in the bank vole (Clethrionomys glareolus). Toxicol. Lett., 147, 229-235.

Krezel, A., Maret, W. (2007). Different redox states of metallothionein/thionein in biological tissue. Biochem. J., 402, 551-558.

Kroncke, R.D. (2001). Zinc finger proteins as molecular targents for nitric oxide-mediated gene regulation. Antioxid. Redox Signal., 3, 565-575.

Kubli, D.A., Quinsay, M.N., Huang, C., Lee, Y., Gustafsson , A.B. (2008). Bnip3 functions as a mitochondrial sensor of oxidative stress during myocardial ischemia and reperfusion. Am. J. Physiol. Heart Circ. Physiol., 295, H2025–H2031.

Krupyansky, Yu.F., Goldansky, V.I. (2002). Energetic landscape in proteins. Chem. Rev. (Russ), 172, 1247-1256.

Laity, J.H., Lee, B.M., Wright, P.E. (2001). Zinc finger proteins new insights into structural and functional oliversity. Curr. Opin. Struct. Biol., 11, 39-46.

Landis-Piwowar, K.R., Milacis, V., Chen, D., Yang, H., Zhao, Y., Chan, T.H., Yan, B., Dou, P.Q. (2006). The proteasome as a potential target for novel anticancer drugs and chemosensitizers. Drug Resist. Updates, 9, 263-273.

Laube, B. (2002). Potentiation of inhibitory glycinergic neurotransmission by Zn^{2+} a synergistic interplay between presynaptic P2X2 and post-synaptic glycine receptors. Eur. J. Neurosci., 16, 1025-1036.

Le, M.T., Teh, C., Shyh-Chang, N., Xie, H., Zhou, B., Korzh, V., Lodish, H.F., Lim, B. (2009). MicroRNA-125b is a novel negative regulator of p53. Genes Dev., 23, 862–876.

Lee, J.T., Gu, W. (2010). The multiple levels of regulation by p53 ubiquitination. Cell Death Differ. 17, 86–92.

Lecane, P.S., Karaman, M.W., Sirisawad, M., Naumovski, L., Miller, R.A., Hacia, J.G., Magda, D. (2005). Motexafin gadolinium and zinc induce oxidative stress responses and apoptosis in B-cell lymphoma lines. Cancer Res., 65, 11676–11688.

Lefaix, J.L., Delanian, S., Leplat, J.J., Tricaud, Y., Martin, M., Nimrod, A., Baillet, F., Daburon, F. (1996). Successful treatment of radiation-induced fibrosis using Cu,Zn-SOD and Mn-SOD: an experimental study. Int. J. Rad. Oncol. Biol. Phys., 35, 305-312.

Lehmann, H.M., Brothwell, B.B., Volak, L.P., Bobilya, D.J. (2002). Zinc status influences zinc transport by porcine brain capillary endotelial cells. J. Nutr., 132, 2763-2768.

Lekli, I., Gurusamy, N., Ray, D., Tosaki, A., Das, D. (2009). Redox regulation of stem cell mobilization. Can. J. Physiol. Pharmacol., 87, 989–995.

Leszczyszyn, O.I., Zeitoun-Ghandour, S., Stuerzenbaum, S.R., Blindauer, C.A. (2011). Tools for metal ion sorting: in vitro evidence for partitioning of zinc and cadmium in C. elegans metallothionein isoforms. Chem. Comm., Doi: 10.1039/c0cc02188A.

Leszczyszyn, O.I., Blindauer, C.A. (2010). Zinc transfer from the embryo-specific metallothionein EC from wheat: a case study. Phys. Chem. Chem. Phys., 12, 13408-13418.

Leszczyszyn, O.I., White, C.R.J., Blindauer, C.A. (2010). The isolated Cys2His2 site in EC metallothionein mediates metal-specific protein folding. Mol. BioSyst., 6, 1592–1603.

Li, F., Bae, B.C., Na, K. (2010). Acetylated hyaluronic acid/photosensitizer conjugate for the preparation of nanogels with controllable phototoxicity: synthesis, characterization, autophotoquenching properties, and in vitro phototoxicity against HeLa Cells. Bioconjugate Chem., 21, 1312–1320.

Li, L., Zhou, D., Peijnenburg, W.J.G., vanGestel, C.A., Jin, S., Wang, Q. (2010). Uptake pathway and toxicity of Cd and Zn in the earthworm *Eisenia fetida*. Soil Biol. Biochem., 42, 1045-1050.

Lilling, C.H., Lonn, M.E., Enoksson, M., Fernandes, A.P., Holmgren, A. (2004). Short interfering RNA-mediated silencing of glutaredoxin 2 increases the sensitivity of HeLa cells toward doxorubicin and phenylarsine oxide. Proc. Natl. Acad. Sci. USA, 101, 13227-13232.

Lim, K.S., Won, Y.W., Park, Y.S., Kim, Y.H. (2010). Preparation and functional analysis of recombinant protein transduction domain-metallothionein fusion proteins. Biochim., 92, 964-970.

Lin, A.M.Y., Fan, S.F., Yang, D.M., Hsu, L.L., Yang, C.H. (2003). Zinc-induced apoptosis in substantia nigra of rat brain: neuroprotection by vitamin D3. Free Radical Biol. Med., 34, 1416-1425.

Loh, S. (2010). The missing Zinc: p53 misfolding and cancer. Metallomics, 2, 442-449.

Lohmann, R.D., Beyersmann, D. (1993). Cadmium and zinc mediated change of the Ca(2+)-dependent endonuclease in apoptosis. Biochem. Biophys. Res. Commun., 190, 1097-10103.

Lopes, U.G., Erhardt, P., Yao, R., Cooper, G.M. (1997). p53-dependent induction of apoptosis by proteasome inhibitors. J. Biol. Chem., 272, 12893-12896.

Loor, G., Kondapalli, J., Schriewer, J.M., Chandel, N.S., Vanden Hoek, T.L., Schumacker, P.T. (2010). Menadione triggers cell death through ROS-dependent mechanisms involving PARP activation without requiring apoptosis. Free Radic. Biol. Med., 49, 1925–1936.

Loui, A., Raab, A., Maier, R., Bratter, P., Obladen, M. (2010). Trace elements and antioxidant enzymes in extremely low birthweight infants. J. Trace Elements Med. Biol., 24, 111–118.

Lushnikov, E.F., Zagrebin, V.M. (1987). Apoptosis: morphology, Biological role mechanisms of development. Arch. Pathol. (Russ.), 49, 84-89.

Lushnikov, E.F., Abrosimov, A.Ju. (2001). Cell death (apoptosis). Ed. Medicine, Moscow.

Lyubartseva, G., Smith, J.L., Markesbery, W.R., Lovell, M.A. (2009). Alterations of zinc transporter proteins ZnT-1, ZnT-4 and ZnT-6 in preclinical Alzheimer's disease brain. Brain Pathol., 20, 343-350.

Mackenzie, G.G., Zago, M.P., Keen, C.L., Oteiza, P.I. (2002). Low intracellular zinc impairs the translocation of activated NF-kappaB to the nuclei in human neuroblastoma IMR-32 cells. J. Biol. Chem., 277, 34610-34617.

Mackenzie, G.G., Zago, M.P., Erlejman, A.G., Aimo, L., Keen, C.L., Oteiza, P.I. (2004). A decrease in neuronal zinc triggers the oxidant-mediated activation of NF-jB and AP-1 in neuroblastoma cells. Free Radic. Biol. Med., 36, S87-S89.

Madala, P.K., Tyndall, J.D.A., Nall, T., Fairlie, D.P. (2010). Update 1 of: proteases universally recognize beta strands in their active sites. Chem. Rev., 110, R1–R31.

Madhavan, L., Ourednik, V., Ourednik, J. (2008). Neural stem/progenitor cells initiate the formation of cellular networks that provide neuroprotection by growth factor-modulated antioxidant expression. Stem Cells, 26, 254–265.

Magaraggia, M., Visona, A., Furlan, A., Pagnan, A., Miotto, G., Tognon, G., Jori, G. (2006). Inactivation of vascular smooth muscle cells photosensitized by liposome-delivered Zn(II)-phthalocyanine. J. Photochem. Photobiol. B, 82, 53-58.

Magda, D., Lecane, P., Wang, Z., Hu, W., Thiemann, P., Ma, X., Dranchak, P.K., Wang, X., Lynch, V., Wei, W., Csokai, V., Hacia, J.G., Sessler, J.L. (2008). Synthesis and anticancer properties of water-soluble zinc ionophores. Cancer Res., 68, 5318–5325.

Majumder, S., Ghoshal, K., Summers, D., Bai, S., Datta, J., Jacob, T. (2003). Chromium(VI) down-regulated heavy metal-induced metallothionein gene transcription by modifying

transactivation potential of the key transcription factor, metalresponsive transcription factor 1. J. Biol. Chem., 278, 26216-26226.
Mantyh, P.W., Ghlardi, J.R., Rogers, S., DeMaster, E., Allen, C.J., Stimson, E.R., Maggio, J.E. (1993). Brain-metal ions aluminium-iron-zinc. J. Neurochem., 61, 1171-1174.
Marino, J., Vior, M.C.G., Dicelio, L.E., Roguin, L.P., Awruch, J. (2010). Photodynamic effects of isosteric water-soluble phthalocyanines on human nasopharynx KB carcinoma cells. Eur. J. Med. Chem., 45, 4129-4139.
Maret, W., Jacob, C., Valle, B.L., Fisher, E.H. (1999). Inhibitory sites in enzymes: zinc removal and reavtivation by thionein. Proc. Natl. Acad. Sci. USA. 96, 1936-1940.
Maret, W. (2008). Metallothionein redox biology in the cytoprotective and cytotoxic functions of zinc. Exp. Gerontol., 43, 363–369.
Maret, W. (2009). Molecular aspects of human cellular zinc homeostasis: redox control of zinc potentials and zinc signals. Biometalls, 22, 149-157.
Maret, W., Li, Y. (2009). Coordination dynamics of zinc in proteins. Chem. Rev., 109, 4682–4707.
Maret, W. (2010). Metalloproteomics, metalloproteomes, and the annotation of metalloproteins, Metallomics, 2, 117–125.
Maret, W. (2011). Metals on the move: zinc ions in cellular regulation and in the coordination dynamics of zinc proteins. Biometals, doi 10.1007/s10534-010-9406-1.
Martin, L.J., Gertz, B., Pan, Y., Price, A.C., Molkentin, J.D., Chang, Q. (2009). The mitochondrial permeability transition pore in motor neurons: involvement in the pathobiology of ALS mice. Exp. Neurol., 218, 333–346.
Martin, M., Allan, L.A., Lickrish, M., Sampson, C., Morrice, N., Clarke, P.R. (2005). Protein kinase A regulates caspase-9 activation by Araf-1 downstream of cytochrome C. J. Biol. Chem., 280, 15449-15455.
Mates, M., Sanchez-Jimenez, F.M. (2001). Role of reactive species in apoptosis implication for cancer therapy. Free Radic. Biol. Med., 30, 1319-1327.
Masuda, Y., Piao, J., Kamiya, K. (2010). DNA Replication-Coupled PCNA Mono-Ubiquitination and Polymerase Switching in a Human In Vitro System. J. Mol. Biol., 396, 487–500.
Medici, V., Santon, A., Sturniolo, G.C., Inca, R.D., Giannetto, S., Albergoni, V., Irato, P. (2002). Metallothionein and antioxidant enzymes in Long Evans Cinnamon rats treated with zinc. Arch. Toxicol., 76, 509-516.
Milicic, V., Chen, D., Giovagnini, L., Diez, A., Fregona, D., Dou, Q.P. (2008). Pyrrolidine dithiocarbamate-zinc(II) and –copper(II) complexes induce apoptosis in tumor cells by inhibiting the proteasomal activity. Toxicol. Appl. Pharmacol., 231, 24-33.
Minami, T., Miyata, E., Sakamoto, Y., Kohama, A., Yamazaki, H., Ishida, S. (2009). Expression of metallothionein mRNAs on mouse cerebellum microglia cells by merosal and its metabolites. Toxicol., 261, 25-32.
Minguet, E.G., Vera-Sirera, F., Marina, A., Carbonell, J. (2008). Evolutionary diversification in polyamine biosynthesis. Mol. Biol. Evol., 25, 2119-2128.
Mocchegiani, E., Giacconi, R., Cipriano, C., Muzzioli, M., Fattoretti, P., Bertoni-Freddari, C., Isani, G., Zambenedetti, P., Zatta, P. (2001). Zinc bound metallothioneins as potential biological markers of aging. Brain Res. Bull., 55, 147-153.
Mocchegiani, E., Bertoni-Freddari, C., Marcellini, F., Malavolta, M. (2005). Brain, aging and neurodegeneration. Role of zinc ion availability. Prog. Neurobiol., 75, 367-390.
Mourelatos, Z., Yachnis, A., Rorke, L., Mikol, J., Gonatas, N.K. (1993). The Golgi apparatus of motor neurons in amyotrphic lateral sclerosis. Ann. Neurol., 33, 608-615.
Mullauer, L., Gruber, P., Sebinger, D., Buch, J., Wohlfart, S., Chott, A. (2001). Mutations in apoptosis genes: a pathogenetic factor for human disease. Mutation Res., 488, 211-231.

Mulligan, V.K., Kerman, A., Ho, S., Chakrabartty, A. (2008). Zinc-Deficient Monomers of Cu/Zn-superoxide dismutase: Implications for Pathogenesis in amyotrophic lateral sclerosis. J. Mol. Biol., 383, 424-436.

Nakabeppu, Y., Oka, S., Sheng, Z., Tsuchimoto, D., Sakumi, K. (2010). Programmed cell death triggered by nucleotide pool damage and its prevention by MutT homolog-1 (MTH1) with oxidized purine nucleoside triphosphatase. Mutation Res., 703, 51–58.

Nakashima, K., Zhou, X., Kunkel, G., Zhang, Z., Behringer, R.R., de Crombrugghe, B. (2002). The novel zinc-finger-containing transcription factor osterix is required for osteoblast differentiation and bone forenation. Cell, 108, 17-29.

Nalepa, G., Rolfe, M., Harper, J.W. (2006). Drug discovery in the ubiquitin- proteasome system. Nat. Rev. Drug Discovery, 5, 596-613.

Nelson, S., Kolls, J.K. (2002). Alcohol, host defense and society. Nat. Rev. Immunol., 2, 205-209.

Nishiyama, N., Stapert, H.R., Zhang, G.D., Takasu, D., Jiang, D.L., Hagano, T., Aida, T., Kataoka, K. (2003). Light harvesting ionic dendrimer porphyrins as new photosensitizers for photodynamic therapy. Bioconj. Chem., 14, 58-60.

Nodera, M., Yanagisawa, H., Wada, O. (2001). Apoptosis. Life Sci., 69, 1639-1649.

Nowak, R.J., Cuny, G.D., Choi, S., Lansbury, P.T., Ray, S.S. (2010). Improving Binding Specificity of Pharmacological Chaperones That Target Mutant Superoxide Dismutase-1 Linked to Familial Amyotrophic Lateral Sclerosis Using Computational Methods. J. Med. Chem. 53, 2709–2718.

Nydegger, I., Rumschik, S.M., Kay, A.R. (2010). Zinc is externalized rather than released during synaptic transmission. ACSChem. Neurosci, 1, 728-736.

O'Hagan, K.A., Cocchiglia, S., Zhdanov, A.V., Tambuwala, M.M., Cummins, E.P., Monfared, M. (2009). PGC-1alpha is coupled to HIF-1 alpha-dependent gene expression by increasing mitochondrial oxygen consumption in skeletal muscle cells. Proc. Natl. Acad. Sci. USA, 106, 2188–2193.

Ohnishi, S., Takano, K. (2004). Amyloid fibrils from the view point of protein folding. Cell Mol. Life Sci., 61, 511-524.

de Oliveira, C.A., Kohn, L.K., Antonio, M.A., Carvalho, J.E., Moreira, M.R., Machado, A.E.H., Pessine, F.B.T. (2010). Photoinactivation of different human tumor cell lines and sheep red blood cells in vitro by liposome-bound Zn(II) Phthalocyanine: Effects of cholesterol. J. Photochem. Photobiol. B: Biol., 100, 92–99.

Olteanu, A., Patel, C.N., Dedmon, M.M., Kennedy, S., Linhoff, M.W., Minder, C.M., Potts, P.R., Deshmukh, M., Pielak, C.J. (2003). Stability and apoptotic activity of recombinant human cytochrome C. Biochem. Biophys. Res. Commun. , 312, 733-740.

D`Orazio, N., Battistoni, A., Stroppolo, M.E., Desideri, A. (2000). Single mutation induces a metal-dependent subunit association in dimeric Cu,Zn-superoxide dismutase. Biochem. Biophys. Res. Commun., 272, 81-83.

Orlov, A. P., Kuznetsov, D. A., Chekhonin, V. P., Buchachenko, A. L., Kuznetsov, V. P. (2011). Nuclear spin selective biochemistry. Isotope effect of zinc-67 in the ATP enzymatic synthesis. In: Proceedings of the 7th International Conference on Chemistry and Biology of Isotope Effects (ISOTOPES-2011), Univ. of Nantes Press: Greoux-les-Bains, p. 27.

Orlova, M.A., Khushpulian, D.M., Orlov, A.P. (2009). The stability of plant peroxidases under irradiation by sources of different nature and power. The role of mutations for changes of conformation state. Bull. Moscow Univ., Chem. (Russ.), 50, 369-377.

Orlova, M.A., Kuznetsov, D.A., Latysheva, A.V., Orlov, A.P. (2009). Creatine kinase radiation stability for Mg-25-rich enzyme. Radiobiol. Radioecol. (Russ.), 49, 580-584.

Orlowski, R.Z., Dees, E.C. (2003). Applying drugs that affect the ubiquitin-proteasome pathway to the therapy of breast cancer. Breast Cancer, 5, 1-7.

Osipova, E.V. (2005). The role of chemical elements in function of central nervous system. Bull. East-Sibir. Sci. Centre, Sibir. Dep. RAMS (Russ.), 1, 79-84.
Oteiza, P.I., Mackenzie, G.G. (2005). Zinc, oxidant-triggered cell signaling and human health. Mol. Aspects Med., 26, 245-255.
Outten, C.E., O'Halloran, T.V. (2001). Femtomolar sensitivity of metalloregulatory proteins controlling zinc homeostasis. Science, 292, 2488–2492.
Owsianowski, E., Walter, D., Fahrenkrog, B. (2008). Negative regulation of apoptosis in yeast. Biochim. Biophys. Acta, 1783, 1303-1310.
Palmiter, R.D., Cole, T.B., Findley, S.D. (1996). ZnT2, a mammalian protein that confers to zinc by facilitating vesicular sequestration. EMBO J., 15, 1784-1787.
Palmiter, R.D. (1998). The elusive function of metallothioneins. Proc. Natl. Acad. Sci. USA, 95, 8428-8430.
Parat, M., Richard, M.J., Polett, S., Hadjur, C., Favier, A., Beani, J.C. (1997). Zinc and DNA fragmentation in keratinocyte apoptosis: its inhibitory effect in UVB irradiated cell. J. Photochem. Photobiol. (Biol.), 37, 101-106.
Parkin, G. (2004). Chemistry. Zinc-zinc bonds a new frontier. Science., 305, 1117-1118.
Parrado, A., Robledo, M., Moya-Quiles, M.R., Marin, L., Chomienne, C., Padua, R.A., Alvarez-Lopez, M. (2004). The promyelocytic leukemia zinc finger protein down-regulates apoptosis and expression of the proapoptotic BID protein in lymphocytes. Proc. Nat. Acad. Sci. USA, 101, 1898-1903.
Patricia, O., Michel, S., Paola, C.Z., Carl, L.K. (2000). Zinc deficiency induced oxidative stress and AP-1 activation in 3T3 cells. Free Radic. Biol. Med., 28, 1091-1099.
Penkowa, M., Florit, S., Giralt, M., Quintana, A., Molinero, A., Carrasco, J., Hidalgo, J. (2005). Metallothionein reduces central nervous system inflammation, neurodegeneration and cell death following kainic acid-unduced epileptic seizures. J. Neurosci., 79, 522-534.
Portt, L., Norman, G., Clapp, C., Greenwood, M.T. (2011). Anti-apoptosis and cell survival: A review. Biochim. Biophys. Acta, 1813, 238-259.
Powell, S.R. (2000). The antioxidant properties of zinc. J. Nutr., 130, 1447S-1451S.
Prasad, A.S. (1998). Zinc and immunity. Mol. Cell. Biochem., 188, 63-69.
Prasuhn, D.E., Feltz, A., Blanco-Canosa, J.B., Susumu, K., Stewart, M.H., Mei, B.C., Yakovlev, A.V., Louko, C., Mallet, J.-M., Oheim, M., Dawson, P.E., Medintz, I.L. (2010). Quantum dot peptide biosensors for monitoring caspase 3 proteolysis and calcium ions. Acs. Nano, 4, 5487-5497.
Premanathan, M., Karthikeyan, K., Jeyasubramanian, K., Manivannan, G. (2011). Selective toxicity of ZnO nanoparticles toward gram-positive bacteria and cancer cells by apoptosis through lipid peroxidation. Nanomed. Nanotechnol. Biol. Med., 7, 184-192.
Provinciali, M., Di Stefano, G., Fabric, N. (1995). Dose-dependent opposite effect of Zn on apoptosis in mouse thymocytes. Int. J. Immunopharmacol., 17, 735-744.
Provinciali, M., Donnini, A., Argentati, K., Di Stasio, G., Bartozzi, B., Bernardini, G. (2002). Reactive oxygen species modulate Zn2+-induced apoptosis in cancer cells. Free Radic. Biol. Med., 32, 431-445.
Qi, P.X., Beckman, R.A., Wand, A.J. (1996). Solution structure of horse heart ferricytochrome C and detection of redox related structural change by high-resolution 1HNMR. Biochem., 35, 12275-12286.
Radyuk, S.N., Klichko, V.I., Orr, W.C. (2004). Profiling Cu,Zn-superoxide dismutase expression in Drosophila melanogaster –a critical regulatory role for intron/exon sequence within the coding domain. Gene, 328, 37-48.
Rafalski, V.A., Brunet, A. (2011). Energy metabolism in adult neural stem cell fate. Prog. Neurobiol., 93, 182-203.

Rakhit, R., Crow, J.P., Lepock, J.R., Kondejewski, L.H., Cashman, N.R., Chakrabartty, A. (2004). Monomeric Cu/Zn-superoxide dismutase is a common misfolding intermediate in the oxidation models of sporadic FALS. J. Biol. Chem., 279, 15499-15504.

Ramakrishanan, N., Kalinich, J.F., McClain, D.E. (1996). Ebselen inhibition of apoptosis by reduction of peroxides. Biochem. Pharmacol., 51, 1443-1451.

Raman, N., Jeyamurugan, R., Senthilkumar, R., Rajkapoor, B., Franzblau, S.G. (2010). In vivo and in vitro evaluation of highly specific thiolate carrier group copper(II) and zinc(II) complexes on Ehrlich ascites carcinoma tumor model. Eur. J. Med. Chem., 45, 5438-5451.

Rana, S.V. (2008). Metals and apoptosis: recent developments. J. Trace Elements Med. Biol., 22, 262-284.

Rezaei, K.A., Chen, Y., Cai, J., Sternberg, P. (2008). Modulation of Nrf2-Dependent Antioxidant Functions in the RPE by Zip2, a Zinc Transporter Protein. IOVS, 49, 1665-1670.

Riedl, S.J., Salvesen, G.S. (2007). The apoptosome: signalling platform of cell death. Nat. Rev. Mol. Cell Biol., 8, 405-413.

Rinkenberger, J.L., Korsmeyer, S.J. (1997). Errors of homeostasis and deregulated apoptosis. Curr. Opin. Gen. Dev., 7, 589-596.

Riley, M.R., Boesewetter, D.E., Kim, A.M., Sirvent, F.P. (2003). Effects of metals Cu, Fe, Ni, V, and Zn on rat lung epithelian. Toxicol., 171, 171-184.

Rizzardini, M., Mangolini, A., Lupi, M., Ubezio, P., Bendotti, C., Cantoni, L. (2005). Low levels of ALS-linked Cu/Zn-superoxide dismutase increase the production of reactive oxygen species and cause mitochondrial damage and death in motor neuron-like cells., J. Neurol. Sci., 232, 95-103.

Roberts, B.R., Tainer, J.A., Getzoff, E.D., Malencik, D.A., Anderson, S.R., Bomben, V.C., Meyers, K.R., Karplus, P.A., Beckman, J.S. (2007). Structural characterization of zinc-deficient human superoxide dismutase and implications for ALS. J. Mol. Biol., 373, 877-890.

Rodgers, K.E., Xiong, S., Steer, R., Zerega, G.S. (2000). Effect of angiotensinII on hematopoietic progenitor cell proliferation. Stem Cells, 18, 287-294.

Rodrıguez-Arguelles, M.C., Ferrari, M.B., Bisceglie, F., Pelizzi, C., Pelosi, Pinelli, S., Sassi, M. (2004). Synthesis, characterization and biological activity of Ni, Cu and Zn complexes of isatin hydrazones. J. Inorg. Biochem., 98, 313-321.

Rossi, M., Abbondanza, C., D`Arcangelo, A., Gazzerro, P., Medici, N., Moncharmont, B., Puca, G.A. (2004). The zinc-finger domain of RIZ protein promotes MCF-7 cell proliferation. Cancer Lett., 215, 229-237.

Rousseau, A., Michaund, A., Chauvet, M.T., Lefant, M., Corvol, P. (1995). The hemoregulatory peptide N-acetyl-Ser-Asp-Lys-Pro is a natural and specific substrate of the N-terminal active site of human ACE. J. Biol. Chem., 270, 3656-3661.

Rubin, L.L., Gatchalian, C.L., Rimon, G., Brooks, S.F. (1994). The molecular mechanism of neuronal apoptosis. Curr. Opin. Neurobiol., 4, 696-702.

Rudolf, E., Cervinka, M., Cerman, J. (2005). Zinc has ambiguous effects on chromium (VI)-induced oxidative stress and apoptosis. J. Trace Elements Med. Biol., 18, 251-260.

Rumie-Vittar, N.B., Prucca, C., Strassert, C., Awruch, J., Rivarola, V.A. (2002). Cellular inactivation and antitumor efficacy of a new zinc phthalocyanine with potential use in photodynamic therapy. Biomed. Pharmacotherapy, 56, 498-502.

Saelens, X., Festjens, N., Walle, L.V., vanGurp, M., vanLoo, G., Vandenabeele, P. (2004). Toxic proteins released from mitochondria in cell death. Oncogene, 23, 2861-2874.

Said, L., Banni, M., Kerkeni, A., Said, K., Messaoudi, I. (2010). Influence of combined treatment with zinc and selenium on cadmium induced testicular pathophysiology in rat. Food Chem. Toxicol., 48, 2759–2765.

Sakurai, H., Yoshikaw, Y., Yasui, H. (2008). Current state for the development of metallopharmaceutics and anti-diabetic metal complexes. Chem. Soc. Rev., 37, 2383–2392.

Sankaramanivel, S., Rajaram, A., Rajaram, R. (2010). Zinc protect human peripheral blood lymphocytes from Cr(III)(phenanthroline)3-induced apoptosis. Toxicol. Appl. Pharmacol., 243, 405-419.

Santon, A., Formigari, A., Albergoni, V., Irato, P. (2006). Effect of Zn treatment on wild type and MT-null cell lines in relation to apoptotic and/or necrotic processes and MT isoform gene expression. Biochem. Biophys. Acta, 1763, 305-312.

Sawa, T., Arimoto, H., Akaike, T. (2010). Regulation of redox signaling involving chemical conjugation of protein thiols by nitric oxide and electrophiles. Bioconjugate Chem., 21, 1121-1129.

Schafer, F.Q., Buettner, G.R. (2001). Redox environment of the cell as viewed through the redox-state of the glutathion disulfide/glutathion couple. Free Radic. Biol. Med., 30, 1191-1212.

Schrantz, N., Anffredon, M.T., Bourgeade, M.F., Besnault, L., Leca, G., Vazquez, A. (2001). Zinc mediated-regulation of caspases activity dose dependent inhibition or activation of caspase-3 in the human Burkitt lymphoma B cells. Cell Death Differ., 8, 152-161.

Sekimoto, T., Oda, T., Pozo, F.M., Murakumo, Y., Masutani, C., Hanaoka, F., Yamashita, T. (2010). The Molecular Chaperone Hsp90 Regulates Accumulation of DNA Polymerase h at Replication Stalling Sites in UV-Irradiated Cells. Mol. Cell, 37, 79–89.

Sekler, I., Sensi, S.L., Ersh, M., Finkel, W.F. Silverman (2007). Mechanism and regulation of cellular zinc transport. Mol. Med., 13, 337-343.

Sensi, S.L., Canzoniero, L.M., Yu, S.P., Ying, H.S., Koh, J.Y., Kerchner, G.A., Choi, D.W. (1997). Measurement of intracellular free zinc in living cortical neurons: routes of entry. J. Neurosci., 17, 9554-9564.

Seve, M., Chimienti, F., Favier, A. (2002). Role du zinc intracellulaire dans la mort cellulaire programmee. Pathol. Biol., 50, 212-221.

Seve, M., Chimienti, F., Devergnas, S., Favier, A. (2004). In silico identification and expression of SLC30 family genes: an expressed sequence tag data mining strategy for the characterization of zinc transpoter`s tissue expression. BMC Genom, 5, 32-36.

Sharif, R., Thomas, P., Zalewski, P., Grahamd, R., Fenech, M. (2011). The effect of zinc sulphate and zinc carnosine on genome stability and cytotoxicity in the WIL2-NS human lymphoblastoid cell line. Mutat. Res., 720, 22-33.

Sharma, U., Rhaleb, N.-E., Pokharel, S., Harding, P., Rasoul, S., Peng, H., Carretero, O. (2008). Novel anti-inflammatory machanisms of N-acetyl-Ser-Asp-Lys-Pro in hypertension-induced target organ damage. Am. J. Phys. Heart Circ. Physiol., 294, H1226-H1232.

Sharma, V., Shukla, R.K., Saxen, N., Parmar, D., Das, M., Dhawan, A. (2009). DNA damaging potential of zinc oxide nanoparticles in human epidermal cell. Toxicol. Lett., 185, 211-218.

Sheiness, D., Bishop, J.M. (1979). DNA and RNA from unifected vertebrate cells contain nucleptide sequences related to the putative transforming gene of avian myelocytomatosis virus. J. Virol, 31, 514-521.

Shi, Y., Toms, B.B., Dixit, N., Kumari, N., Mishra, L., Goodisman, J., Dabrowiak, J.C. (2010). Cytotoxicity of Cu(II) and Zn(II) 2,2′-bipyridyl complexes: dependence of IC50 on Recovery Time. Chem. Res. Toxicol., 23, 1417-1426.

Shvedova, A.A., Kagan, V.E., Fadeel, B. (2010). Close encounters of the small king: adverse effects of man-made materials interfacing with the nano-cosmos of biological systems. Annu. Rev. Pharmacol. Toxicol., 50, 63-88.

Silva, R.D., Sotoca, R., Johansson, B., Ludovico, P., Sansonetty, F., Silva, M.T., Peinado, J.M., Corte-Real, M. (2005). Hyperosmotic stress induces metacaspase- and mitochondria-dependent apoptosis in Saccharomyces cerevisiae. Mol. Microbiol., 58, 824–834.

Skvortsova, V.I., Timofeev, T.P., Shalnova, C.A. (2001a). Involvement of apoptosis in the formation of brain infarction. J. Neurol. Psich. (Russ.), 2, 12-19.

Skvortsova, V.I., Limborska, S.A., Slominski, P.A., Levitskaya, N.I., Levitsky, G.N., Shadrina, M.I. (2001b). Sporadic amyotrophic sclerosis assosiated with the D90A Cu/Zn-superoxide dismutase mutations in Russia. Eur. J. Neurol., 8, 167-172.

Slaby, I., Lind, B., Holmgren, A. (1984). T7 DNA polymerase is not a zinc- metalloenzyme and the polymerase and exonuclease activities are inhibited by zinc ions. Biochem. Biophys. Res. Commun., 122, 1410-1417.

Slater, J.P., Mildvan, A.S., Loeb, L.A. (1971). Zinc in DNA polymerase. Biochem. Biophys. Res. Commun., 44, 37-43.

Soda, K., Dobashi, Y., Kano, Y., Tsujinaka, S., Konishi, F. (2009). Polyamine-rich food decreases age-associated pathology and mortality in aged mice. Exp. Gerontol., 44, 727-732.

Solomons, N.W. (1988). Zinc and cooper. In: “Modern nutrition in health and disease”. Ed. M.E.Shils, V.R.Young. Philadelphia, Lea and Febiger. pp. 238-262.

Spahl, D.U., Berendji-Green, D., Suschek, C.V., Kolb-Bachofen, V., Kroncke, K.D. (2003). Regulation of zinc homeostasis by inducible NO-synthase derived NO nuclear metallothionein translocation and intranuclear Zn^{2+} release. Proc. Natl. Acad. Sci. USA, 100, 13952-13957.

Spesia, M.B., Rovera, M., Durantini, E.N. (2010). Photodynamic inactivation of E.coli and Streptococcus mitis by cationic zinc(II) phthalocyanines in media with blood derivatives. Eur. J. Med. Chem., 45, 2198–2205.

Stennicke, H.R., Salvesen, G.S. (1997). Biochemical characteristics of caspase-3,-6,-8. J .Biol. Chem., 272, 25719-25723.

Strawn, W.B., Richmond, R.S., Ann, T.E., Gallagher, P.E., Ferrario, C.M. (2004). Renin-angiotensin system expression in rat bone marrow haematopoietic and stromal cells. Br. J. Haematol., 126, 120-126.

Streedhar, B., Subramaniyan, R., Nair, K.M. (2004). A protective role for zinc on intestinal peroxidative damage during oral iron repletion. Biochem. Biophys. Res. Commun., 318, 992-997.

Subramanian, J.R., Lyons, W.E., Liu, J., Bartnikas, T.B., Rothstein, J., Price, D.L., Cleveland, D.W., Gitlin, J.D., Wong, P.C. (2002). Mutant SOD1 causes motor neuron disease independent of copper chaperon-mediated copper loading. Nat. Neurosci., 5, 301-307.

Suda, T., Nagata, S. (1994). Purification and characterization of the Fas-ligand that induces apoptosis. J. Exp. Med., 179, 873-877.

Sunderman, F.W. (1995). The influence of zinc on apoptosis. Ann. Clinic. Lab. Sci., 25, 134-142.

Surh, Y. (2004). Cancer chemoprevention with deetary phytochemical. Nat. Rev. Cancer, 3, 768-780.

Swaminath, G., Lee, T.W., Kobilka, B. (2003). Identification of an allosteric binding site for Zn on the beta2 adrenergic receptor. J. Biol. Chem., 278, 352-356.

Swerdlow, R.H. (2002). Mitochondrial DNA-related mitochondrial dysfunction in neurodegenerative diseases. Arch. Pathol. Lab. Med., 126, 271–280.

Swindell, W.R. (2011) Metallothionein and the biology of ageing. Age. Res. Rev., 10, 132-145.

Szeltukhin, A.O., Chumakov, P.M. (2010). Casual and induced functions of p53 gene. Success of Biol. Chem. (Russ.), 50, 447-516.

Szuster-Ciesielska, A., Daniluk, J., Bojarska-Junak, A. (2005). Apoptosis of blood mononuclear cells in alcoholic liver cirrhosis. The influence of in vitro ethanol treatment and zinc supplementation. Toxicol., 212, 124-134.

Tabatabai, N.M., Blumenthal, S.S., Petering, D.H. (2005). Adverse effect of cadmium on binding of transcription factor Sp1 to the GC-rich regions of the mouse sodium-glucose cotransporter 1, SGLT1, promoter. Toxicol., 207, 369–382.

Tamura, T., Sadakata, N., Oda, T., Muramatsu, T. (2002). Role of zinc ions in ricin-induced apoptosis in U937 cells. Toxicol. Lett., 132, 141-151.

Takeda, A. (2000). Movement of zinc and its functional significance in the brain. Brain Res. Brain Res. Rev., 34, 137-148.

Takeda, A. (2001). Zinc homeostasis and functions of zinc in the brain. Biometals, 14, 343-351.

Takeda, A., Suzuki, M., Oku, N. (2002). Possible involvement of plasma histidine in differential brain permeability to zinc and cadmium. Biometals, 15, 371-375.

Takeda, A., Hirate, M., Tamano, H., Oku, N. (2003). Release of glutamate and GABA in the hippocampus under zinc deficiency. J. Neurosci., 72, 537-542.

Tanaka, K., Tsumaki, N., Kozak, C.A., Matsumoto, Y., Nakatani, F., Iwamoto, Y., Yamada, Y. (2002). A Kruppel-associated box zinc-finger protein, NT-2, represses cell-type specific promoter activity of the alpha 2(XI) collagene gene. Mol. Cell Biol., 22, 4256-4267.

Tapler, R., Perini, G., Green, M.R. (2001). Expressing the human genome. Nature, 409, 832-833.

Taylor, C.G., McCutchon, T.L., Boermans, H.J., DiSilvestro, R.A., Bray, T.M. (1997). Comparison of Zn and vitamin E for protection against hyperoxia-induced lung damage. Free Radic. Biol. Med., 22, 543-550.

Taylor, K.M., Morgan, H.E., Johnson, A., Hadly, L.J., Nicholson, R.I. (2003). Structure-function analysis of LIV-1, the breast cancer assosiated protein that belongs to a new subfamily of zinc transporters. Biochem. J., 375, 51-59.

Taylor, S.C., Peers, C. (2000). Tree distinct Ca^{2+} influx pathways couple acetylcholine receptore activation to catecholamine secretion from PC12 cells. J. Neurochem., 75, 1583-1589.

Thevenod, F. (2009). Cadmium and cellular signaling cascades: to be or not to be? Toxicol. Appl. Pharmacol., 238, 221–239.

Torriglia, A., Chaudun, E., Courtois, Y., Counis, M.F. (1997). On the use of Zn2+ to discriminate endonucleases activated during apoptosis. Biochimie., 79, 435-438.

Truong-Tran, A.Q., Ho, L.H., Chai, F., Zalewski, P.D. (2000). Cellular zinc fluxes and the regulation of apoptosis gene directed cell death. J. Nutr., 130(Suppl.), 1459S-1466S.

Truong-Tran, A.Q., Ruffin, R.E., Zalewski, P.D. (2001). The role of zinc in caspase activation and apoptotic cell death. Biometals, 14, 315-330.

Truong-Tran, A.Q., Glosser, D., Ruffin, R.E., Murgia, Ch., Zalewski, P.D. (2003) Apoptosis in the normal and inflamed airway epithelium. Role of zinc in epithelium protection and procaspase-3 regulation. Biochem. Pharmacol., 66, 459-468.

Tuan, J.C., Zhai, W., Comai, L. (1999). Recruitment of TATA-binding protein-TAFI complex SL1 to the human ribosomal DNA promoter is mediated by the carboxy-terminal activation domain of upstream binding factor (UBF) and is regulated by UBF phosphorylation. Mol. Cell. Biol., 19, 2872-2879.

Ukhterova, N.D. (2008). Index of zinc/copper and T-helper function in chronic obstructive pulmonary disease in various biogeochemical conditions. In “Issues of Clinical Medicine” Ed. Chuvachia Univ., Cheboksary, 112-114.

Ukhterova, N.D. (2009). Features of cell immune response in patients with obstructive pulmonary disease in conditions of natural zinc deficiency. Allergol. Immunol. (Russ.), 10, 37-40.

Undergasser, G., Rumpold, H., Plas, E., Witkowski, M., Plister, G., Berger, P. (2000). High levels of zinc ions induce loss of mitochondrial potential and degradation of antiapoptotic Bcl-2 protein in vitro cultivated human prostate epithelian cells. Biochem. Biophys. Res. Commun., 279, 607-614.

Urushidate, S., Matsuzaka, M., Okubo, N., Iwasaki, H., Hasebe, T., Tsuya, R., Iwane, K., Inoue, R., Yamai, K., Danjo, K., Takahashi, I. et al. (2010). Association between concentration of trace elements in serum and bronchial asthma among Japanese general population. J.Trace Elements Med. Biol., 24, 236–242.

Valko, M., Leiter, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol., 39: 44–84.

Valle, B.L., Falchuk, K.H. (1993). The biochemical basis of zinc physiol. Physiol. Rev., 73, 79-118.

Van Sprang, P.A., Janssen, C.R. (2001). Toxicology identification of metals: development of toxicity identification finferprints. Env. Toxicol. Chem., 20, 2604-2610.

Vilborg, A., Glahder, J.A., Wilhelm, M.T., Bersani, C., Corcoran, M., Mahmoudi, S., Rosenstierne, M., Grander, D., Farnebo, M., Norrild, B., Wiman, K.G. (2009). The p53 target Wig-1 regulates p53 mRNA stability through an AU-rich element. Proc. Natl. Acad. Sci. USA, 106, 15756–15761.

Vladimirskaya, E.V. (2002). Mechanisms of apoptotic cell death. Hematol. Transfusiol. (Russ.), 3, 3-11.

Vladimirskaya, E.V. (2007) Mechanisms of hemopoietic and leukemia genesis. Moscow., Ed. Dinastiya. 7-26.

Vogt, K., Mellor, J., Tong, G., Nicoll, R. (2000). The action of synaptically released zinc at hippocampal mossy fiber synapses. Neuron, 26, 187-196.

Waldron, K.J., Robinson, N.J. (2009). How do bacterial cells ensure that metalloprotein get the correct metall? Nat. Rev. Microbiol., 7, 25–35.

Wang, D., Carretero, O.A., Yang, X.-Y., Rhaleb, N.-E., Liu, Y.-H., Liao, T.-D., Yang, X.-P. (2004). N-acetyl-Seryl-Aspartyl-Lysil-Proline stimulates angiogenesis in vitro and in vivo. Am. J. Physiol. Heart Circ. Physiol., 287, H2099-H2105.

Wang, K., Zhou, B., Kuo, Y.M., Zemansky, J., Gitschier, J. (2002). A novel member of a zinc transporter family is detective in acrodermatitis enteropathica. Am. J. Genet., 71, 66-73.

Wang, L., Liu, W., Parker, S.H., Wu, S. (2010). Nitric oxide synthase activation and oxidative stress, but not intracellular zinc dyshomeostasis, regulate ultraviolet B light-induced apoptosis.. Life Sci., 86, 448-454.

Wätjen, W. Haase, H., Biagioli, M., Beyersmann, D. (2000). Induction of apoptosis in mammalian cells by cadmium and zinc. Am. J. Clinic. Nutr., 71, 81-87.

Ward, A.D., Lincoln, S.F., Betts, W.H., Zalewski, P.D., Forbes, I.J., Mahadevan. (2000). Zinquin ester – a reagent for the investigation of the role of available Zn II in living systems. In “Trace elements in man and animals” Ed. M. Roussel, R.A. Anderson, A.E. Favier, 995-998.

Wei, T., Chen, C., Hou, J., Xin, W., Mori, A. (2000). Nitric oxide induced oxidative stress and apoptosis in neuronal cells. Biochim. Biophys. Acta Mol. Cell Res., 1498, 72-79.

Weihong, X.U., Wenyi, L.I., Jianping, H.E., Singh, B., Zhiting, X. (2009). Effects of insoluble Zn, Cd and EDTA on the growth, activity of antioxidant enzymes and uptake of Zn and Cd in *Vetiveria zizanioides*. J. Environ. Sci., 21, 186-192.

Weiss, J.H., Sensi, S.L., Koh, J.Y. (2000). Zn^{2+} a novel ionic mediator of neuronal injury in brain disease. Trends Pharmacol. Sci., 21, 395-401.

Wilson, D., Varigos, G., Ackland, M.L. (2006). Apoptosis may underlie the pathology of zinc-deficient skin. Immunol. Cell Biol., 84, 28-37.

Wiseman, D.A., Wells, S.M., Hubbard, M., Welker, J.E., Black, S.M. (2007). Alterations in zinc homeostasis underlie endothelian cell death induced by oxidative stress from acute exposure to hydrogen peroxide. Am. J. Physiol. Lung Cell Mol. Physiol., 292, L165-L177.

Wood, G.P., Osborne, N.N. (2001). The influence of zinc on caspase-3 and DNA breakdown in cultured human retinal pigment epithelial cells. Arch. Ophtamol., 119, 81-88.

Woster, P.M. (2006). Polyamine structure and synthetic analogs. In: Polyamine Cell Signaling, Physiology, Pharmacology and Cancer Research. J.Y.Wang, R.A.Casero, Ed., Humana Press: Totowa, NJ, 3-24.

Wright, D.T., Cohn, L.A., Li, H., Fisher, B., Li, C., Alder, K.B. (1994). Interactions of oxigen radicals with airway epithelium. Envir.Health Perspect., 102(Suppl.), 85-90.

Wu, H., Xing, K., Lou, M.F. (2010). Glutaredoxin2 prevents H2O2-induced cell apoptosis by protecting complex I activity in the mitochondria. Biochem. Biol. Acta, 1797, 1705-1715.

Wu, W., Wang, X., Zhang, W., Reed, W., Samet, J.M., Whang, Y.E. (2003). Zinc-induced PTEN protein degradation through the proteasome pathway in human airway epithelian cells. J. Biol. Chem., 278, 28258-28263.

Wyllie, A.H. (2010). Where, o death, is thy sting? - a brief review of apoptosis biology. Mol. Neurobiol., 42, 4–9.

Xiao, Z., Wedd, A.G. (2010). The challenges of determining metal–protein affinities. Nat. Prod. Rep., 27, 768-789.

Xie, S., Lin, H., Sun, T., Arlinghaus, R.B. (2002). Jack 2 is involved in c-myc induction by Bcr-Abl. Oncogene, 21, 7137-7146.

Xu, G., Huang, Y., Rich, R.L., Myszka, D.G., Cinlli, M. (2001). Covalent inhibition revealed by the crystal structure of the caspase-8/p35 complex. Nature, 410, 494-496.

Yin, H., Casey, P.S., McCall, M.J., Fenech, M. (2010). Effects of Surface Chemistry on Cytotoxicity, Genotoxicity, and the Generation of Reactive Oxygen Species Induced by ZnO Nanoparticles. Langmuir, 26, 15399-15408.

Yoshitake, S., Nanri, H., Fernando, M.R., Minakami, S. (1994). Possible differences in the regenerative roles played by thiotransferase and thioredoxine for oxidatively damaged proteins. J. Biochem., 116, 42-46.

Yu, H., Zhou, Y., Lind, S.E., Ding, W.Q. (2009). Clioquinol targets zinc to lysosomes in human cancer cells. Biochem. J., 417, 133–139.

Yu, S.W., Andrabi, S.A., Wang, H., Kim, N.S., Poirier, G.G., Dawson, T.M., Dawson, L. (2006). Apoptosis-inducing factor mediates poly(ADP-ribose) (PAR) polymer-induced cell death. Proc. Natl. Acad. Sci., 103, 18314–1831.

Yu, R.-A., Xia, T., Wang, A., Chen, X. (2006). Effects of Selenium and Zinc on Renal Oxidative Stress and Apoptosis Induced by Fluoride in Rats. Biomed. Envir. Sci., 19, 439-444.

Yu, T., Wang, X., Purring-Koch, C., Wei, Y., McLendon, G.L. (2001). A mutational epitope for cytochrome C binding to the apoptosis protease activation factor-1. J. Biol. Chem., 276, 13034-13038.

Zago, M.P., Oteiza, P.I. (2001). The antioxidant properties of zinc: interactions with iron and antioxidants. Free Radic. Biol. Med., 31, 266-274.

Zalewski, P.D., Truong-Tran, A.T., Grosser, D., Jayaram, L., Murgia, C., Ruffin, R. (2005). Zinc metabolism in airway epithelium and airway inflammation: basic mechanisms and clinical targets. Pharmacol. Therap., 105, 127-149.

Zalzman, M., Falco, G., Sharova, L., Nishiyama, A., Thomas, M., Lee, S., Stagg, C.A., Hoang, H.G., Yang, H., Indig, F.E., Wersto, R.P., Ko, M.S. (2010). Zscan4 regulates telomere elongation and genomic stability in ES cells. Nature, 464, 858-863.

Zhang, J., Chen, X. (2008). Posttranscriptional regulation of p53 and its targets by RNA binding proteins. Curr. Mol. Med., 8, 845–849.

Zhang, H., Joseph, J., Crow, J., Kalyanaraman, B. (2004). Mass spectral evidence for carbonate-anion-radical-induced posttranslational modification of tryptophan to kynurenine human Cu,Zn superoxide dismutase. Free Radic. Biol. Med., 36, 2018-2026.

Zhang, S.J., Steijaert, M.N., Lau, D., Schutz, G., Delucinge-Vivier, C., Descombes, P., Bading, H. (2007). Decoding NMDA receptor signaling: identification of genomic programs specifying neuronal survival and death. Neuron, 53, 549–562.

Zhang, Y., Herman, B. (2002). Ageing and apoptosis. Mech. Ageing Develop. 123, 245-260.

Zhao, R., Planalp, R., Ma, R., Greene, B.T., Jones, B.T., Brechbiel, M.W., Torti, F.M., Torti, S.V. (2004). Role of zinc and iron chelation in apoptosis mediated by tachpyridine, an anti-cancer iron chelator. Biochem. Pharmacol., 67, 1677-1688.

Zheng, J., Lou, J.R., Zhang, X., Benbrook, D.M., Hanigan, M.H., Lind, S.E., Ding, W.D. (2010). N-Acetylcysteine interacts with copper to generate hydrogen peroxide and selectively induce cancer cell death. Cancer Lett., 298, 186–194.

Zhou, C., Shunji, D., Jinsheng, L., Junlin, G., Jori, G., Milanesi, C. (1996). Apoptosis of mouse MS-2 fibrosarcoma cells induced by photodynamic therapy with Zn(II)-phthalocyanine. J. Photochem. Photobiol., B Biol., 33, 219-223.

Zivny, J., Klener, P., Pytlik, R., Andera, L. (2010). The role of apoptosis in cancer: development and tratment of hematologic malignancies. Curr. Pharm. Design., 16, 11-33.

Zsembery, A., Fortenberry, J.A., Liang, L., Bebok, Z., Tucker, T.A., Boyce, A.T. (2004). Extracellulare zinc and ATP restore chloride secretion across cytic fibrosis airway epithelia by triggering calcium entry. J. Biol. Chem., 279, 10720-10729.