

Selenoproteins and their emerging roles in signaling pathways

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The functional activity of selenoproteins has a wide range of effects on complex pathogenetic processes, including teratogenesis, immuno-inflammatory, neurodegenerative. Being active participants and promoters of many signaling pathways, selenoproteins support the lively interest of a wide scientific community. This review is devoted to the analysis of recent data describing the participation of selenoproteins in various molecular interactions mediating important signaling pathways. Data processing was carried out by the method of complex analysis. For convenience, all selenoproteins were divided into groups depending on their location and function. Among the group of selenoproteins of the ER membrane, selenoprotein N affects the absorption of Ca^{2+} by the endoplasmic reticulum mediated by oxidoreductin (ERO1), a key player in the CHOP/ERO1 branch, a pathogenic mechanism that causes myopathy. Another selenoprotein of the ER membrane selenoprotein K binding to the DHHC6 protein affects the IP3R receptor that regulates Ca^{2+} flux. Selenoprotein K is able to affect another protein of the endoplasmic reticulum CHERP, also appearing in Ca^{2+} transport. Selenoprotein S, associated with the lumen of ER, is able to influence the VCP protein, which ensures the incorporation of selenoprotein K into the ER membrane. Selenoprotein M, as an ER lumen protein, affects the phosphorylation of STAT3 by leptin, which confirms that Sel M is a positive regulator of leptin signaling. Selenoprotein S also related to luminal selenoproteins ER is a modulator of the IRE1 α -sXBP1 signaling pathway. Nuclear selenoprotein H will directly affect the suppressor of malignant tumours, p53 protein, the activation of which increases with Sel H deficiency. The same selenoprotein is involved in redox regulation. Among the cytoplasmic selenoproteins, abundant investigations are devoted to Selp, which affects the PI3K/Akt/Erk signaling pathway during ischemia/reperfusion, is transported into the myoblasts through the plasmalemma after binding to the apoER2 receptor, and into the neurons to the megaline receptor and in general, selenoprotein P plays the role of a pool that stores the necessary trace element and releases it, if necessary, for vital selenoproteins. The thioredoxin reductase family plays a key role in the invasion and metastasis of salivary adenoid cystic carcinoma through the influence on the TGF- β -Akt/GSK-3 β pathway during epithelial-mesenchymal transition. The deletion of thioredoxin reductase 1 affects the levels of messengers of the Wnt/ β -catenin signaling pathway. No less studied is the glutathione peroxidase group, of which GPX3 is able to inhibit signaling in the Wnt/ β -catenin pathway and thereby inhibit thyroid metastasis, as well as suppress protein levels in the PI3K/Akt/c-fos pathway. A key observation is that in cases of carcinogenesis, a decrease in GPX3 and its hypermethylation are almost always found. Among deiodinases, deiodinase 3 acts as a promoter of the oncogenes BRAF, MEK or p38, while stimulating a decrease in the expression of cyclin D1. The dependence of the level of deiodinase 3 on the Hedgehog (SHH) signaling pathway is also noted. Methionine sulfoxide reductase A can compete for the uptake of ubiquitin, reduce p38, JNK and ERK promoters of the MAPK signaling pathway; methionine sulfoxide reductase B1 suppresses MAPK signaling messengers, and also increases PARP and caspase 3.

Keywords: functions of selenoproteins; cytoplasm selenoproteins; thioredoxin reductases; glutathione peroxidases; methionine sulfoxide reductases; carcinogenesis.

Introduction

To date, a cluster of selenoproteins, including 25 species, is being actively studied due to the involvement of these compounds in a number of important biomolecular mechanisms that affect pathogenetic processes such as carcinogenesis, oxidative stress, inflammation, and neurodegeneration.

So, the search for ways to influence the expression of selenoproteins with the aim of controlling some teratogenic processes is currently underway. One of these is an attempt to inactivate the UGA gene and tRNA, which encode and translate accordingly the selenocysteine residue, which is part of all selenoproteins. A number of authors have found that Cas9-sgRNA ribonucleoproteins using the CRISPR technique can induce efficient genome editing in Hek293, HepG2, HaCaT, HAP1, HeLa, and LNCaP cell cultures, which causes a strong decrease in the expression of selenoproteins (Vindry et al., 2019). Attempts to study the basics of controlling selenoprotein regulators are carried out not only through gene modifications, but also by determining the role of gene

polymorphism. A number of works are devoted to the study of the relationship of genes polymorphisms encoding certain selenoproteins with risks and predictions in the development of tumors. The clinic studied the polymorphism of the gene of selenoprotein (Sep15), which is a selenocysteine-containing oxidoreductase, in women with breast cancer. Clinical and pathological parameters such as age, stage of disease, tumour type, classification and receptor status did not reveal a connection with polymorphism for this gene. Selenoprotein gene polymorphism (Sep15) did not affect the risk of breast cancer. (Watrowski et al., 2016). However, in the case of diabetes, it was found that genetic polymorphism for selenoprotein S is associated with type 2 diabetes (Zhao et al., 2018).

A number of promoters are involved in the mechanism of selenoproteins expression regulation, through the action of which selenoprotein activity can also be controlled. Thus, in the model of the C28/I2 chondrocyte cell line, sufficient expression of SBP2 (selenocysteine binding protein) and miR-181a-5p (one of the post-transcriptional gene expression regulators) was detected under conditions of normal Se con-

tent and vice versa, insufficient expression was revealed in case of Se deficiency. miR-181a-5p regulates SBP2 in the chondrocyte model. It is miR-181a-5p that is more sensitive to Se deficiency. Thus, a mechanism for reducing the expression of selenoproteins through the effect on selenocysteine-binding protein and miR-181a-5p was revealed (Min et al., 2018).

The existence of selenoproteins also depends on another promoter, which has caused interest due its influence on the signaling pathway that regulates the proliferative and migratory abilities of cells. The biosynthesis of selenocysteine included in selenoproteins is regulated by the Tmau1ap protein, the deficiency of which inhibits the proliferation of cardiomyocyte-like cells. On the model of NIH3T3, JEG-3, and Bewo cells (embryonic, trophoblastic, and placental, respectively), a decrease in the expression of selenoproteins determines upon knock-down of the Tmau1ap protein. Along with this, a decrease in the proliferation and migration of cells of these groups is noted. Inhibition of Akt phosphorylation (a member of the protein kinase family, a key player of the PI3K/Akt signaling pathway) in the PI3K/Akt signaling pathway is observed. Thus, the Tmau1ap protein modulates the PI3K/Akt signaling pathway and simultaneously affects the expression of selenoproteins, thereby playing an important role in the regulation of cell proliferation and migration in embryogenesis (Hu et al., 2018).

In addition to the above regulatory proteins for the synthesis of selenoproteins, the catalytic activity of selenoproteins depends on the incorporation of the selenocysteine residue. This function is performed by the protein binding (SECISBP2) in parallel affecting the signaling pathway PI3K/Akt and ERK. The authors clarified the role of this protein in trophoblast cells and the molecular mechanism that ensures its function. Turning off SECISBP2 by miRNA transfection reduced levels of only some selenoproteins – GPx1, SelK, Dio2, while MDA (malondialdehyde) levels increased. SECISBP2 silence suppressed the proliferation, migration and invasion of trophoblast cells; significantly reduced the level of β -hCG (β chorionic gonadotropin) and progesterone. Inactivation of the PI3K/Akt and ERK signaling pathways has also been detected (Li et al., 2017).

The participation of selenoproteins in many pathogenetic processes creates an interest in studying the mechanisms and key players in the signaling pathways that mediate this participation with the goal of further therapeutic effects. It has particular importance in the case of teratogenesis. For example the expression of selenoprotein M increases and correlates with late stage, progression and short survival in patients with renal cell carcinoma. In a mouse experiment, deletion of this selenoprotein reduces viability, clonality, and metastasis of renal cancer cells and suppresses tumour growth (Jiang et al., 2019).

Recently, overexpression of M selenoproteins M (SELM) has also been detected in human hepatocellular carcinoma cells. An increase of SELM expression in the liver tissue of hepatocellular carcinoma and a gradual increase in expression are associated with an increase in the level of malignancy. The authors suggest the use of SELM as a putative marker for hepatocellular carcinoma (Guerriero et al., 2014).

The connection of some selenoproteins with specific pathologies initiates attempts to determine their role in the signaling pathways of these pathogenetic processes. So again, researchers point out that selenoproteins can inhibit carcinogenesis by counteracting oxidative damage and mutations. But under conditions of an initially high level of oxidative damage, the activity of selenoproteins can cause resistance to apoptosis and chemotherapy in cancer cells. Plenty of selenoproteins have different effects in signaling pathways such as MAPK, AKT, VEGF and c-Met and others. Thus, the modulation of the pool of selenoproteins by adding Se does not always have a beneficial effect, and in some cases can be harmful (Short & Williams, 2017).

In the epithelium of the prostate gland the expression decrease of a large number selenoproteins provokes oncogenesis. It is achieved by deletion of the gene encoding tRNA Sec selenocysteine residue. The latter one is used for inserting the selenocysteine residue into selenoproteins during their translation. In mice with the sec tRNA gene knockdown, neoplastic changes were detected in all prostate lobes, which progressed to dysplasia and microinvasive cancer. Moreover, the removal of the tumour suppressor and the introduction of the oncogen

are not required to initiate oncogenesis. Simultaneously, there is an increase in lipid peroxidation markers due to a decrease in the antioxidant effect of selenoproteins (Luchman et al., 2014).

And relatively recently, the association of alleles of selenoprotein S and selenoprotein P, glutathione peroxidase 4 with a high risk of aortic occlusion disease and peripheral artery disease has been identified. There is also a summation of the effect of these genes on the risks of abdominal aortic aneurysm and aortic occlusion disease. The relationship of heart failure with the allele SEPP1 and elevated concentrations of SeP is revealed (Strauss et al., 2018).

At the model of heat stress, which suppresses myogenic differentiation and disrupts the development of muscle tubes, the expression of mRNA of 24 genes encoding selenoproteins was studied. Obviously the heat stress enhances the expression of 18 selenoproteins after 4 days of hyperthermia, 11 selenoproteins after 6 days and 8 selenoproteins after 8 days. Only a decrease in the expression of deiodinase 2 was observed after 6 days. Such a reaction to heat stress can be considered as a protective effect of selenoproteins on damage associated with hyperthermia in myoblast cells (Tang et al., 2018).

The data of the some selenoproteins participation in the amyloid- β ($A\beta$) modeling are interesting. So, selenoprotein P (SelP-H) and mutant selenoprotein M (SelM) have ability to bind transition metal ions and modulate Zn^{2+} -mediated amyloid- β ($A\beta$) aggregation, generation of reactive oxygen species and neurotoxicity. Aggregation and cytotoxicity of amyloid- β ($A\beta$) peptide with transition metal ions in neurons take part in the progress of Alzheimer's disease. The binding of $A\beta$ with Zn^{2+} suppress $A\beta$ fibrillation, but the SelP-H and SelM may have significantly restored $A\beta$ fibrillation, which is confirmed by fluorescence and electronic microscopy. Interestingly, both SelP-H and SelM inhibit Zn^{2+} - $A\beta$ -induced neurotoxicity and intracellular production of reactive oxygen species in living cells. Studies show that SelP and SelM can play prominent roles in regulating redox balance as well as metallic homeostasis (Du et al., 2013).

High expression of selenoprotein T is observed in immature tissues during embryogenesis, and also remains in the endocrine glands, such as the pituitary gland, pancreas, thyroid gland and testes, which indicates the important role of this selenoprotein in the production of hormones. With a baseline low expression of SELENOT in the brain, knock-down of selenoprotein T causes morphological rearrangements of the brain of mice affecting their behaviour. Moreover, enhanced induction of selenoprotein T was found after brain damage, which indicates its protective role. The role of SELENOT in the mechanisms of insulin and corticotropin release has also confirmed (Anouar et al., 2018).

The search for new selenoproteins and the decoding of their amino acid sequence, specific mRNA, expression levels in tissues and organs, and the role in signaling molecular interactions continue. For selenoprotein U, an amino acid sequence of 224 amino acids was described in the chicken model. The same model revealed a decrease in the levels of specific mRNA and expression of U selenoprotein in muscles, liver, kidneys, heart, spleen and lungs of animals with selenium deficiency. At the same time, expression levels in the brain and testes remain unchanged (Jiang et al., 2015).

A connection is established between the level of selenium and the activity of a number of functional systems. The relationship between the membrane transporter ZIP8 and the level of Se in the liver was revealed. ZIP8 knockout mice showed a significant decrease in Se, which leads to the inhibition of selenium-containing glutathioneperoxidase 1 and 2. It was concluded that ZIP8 plays an important role in maintaining normal liver function, probably through the regulation of Se homeostasis and redox balance (Liu et al., 2018).

In most models used to study the functional roles of selenoproteins, mice are used as biological objects. However, the mouse model widely used to study the physiology of selenoproteins has differences compared to humans. So, for example, deletion of the iodothyronine-deiodinase gene causes insignificant phenotypic changes in mice, but is lethal for humans. However, knockdown by thioredoxin reductase 2 and glutathione peroxidase 4 has been lethal for mice, but is easily tolerated by humans. At the same time, knockdown of the glutathione peroxidase gene 1 and 2 is tolerable for both mice and humans, while knockdown

of thioredoxin reductase 1 and selenoprotein T is intolerable for both (Santesmasses et al., 2019).

Studies of the role of selenoproteins are only at an early stage and many attempts must be made to establish accurate molecular signaling mechanisms by which certain selenoproteins affect carcinogenesis, embryogenesis, inflammatory, redox and neurodegenerative processes. Once identified, this knowledge will be projected onto the individual parameters of a person and will allow modulating the complex pathogenetic processes of many diseases. Important in our opinion is maintaining the constant interest of the scientific community in the problem of studying this functionally active group.

The article made an attempt to analyze and systematize the latest ideas about the participation of selenoproteins in signaling pathways.

Signaling pathways mediated by selenoproteins of the ER membrane (Sel N, SelK, SelT)

Recessive genes encode selenoprotein N and RYR1, proteins that regulate skeletal muscle calcium homeostasis, cause severe congenital myopathies. An increase in the level of class II histone deacetylases (HDACs), which cause hypoacetylation and, as a result, repression of the selenoprotein N and RYR1 genes, has been revealed. Along with this, there is an increase in DNA methyltransferases, which catalyze the methylation of nucleotide residues in the DNA, which leads to a change in the properties of DNA, while changing the activity, functions of the corresponding genes, as well as the spatial structure of the nucleic acid. Genomic DNA methylation analysis of patients with RYR1 and SELENON variants revealed more than 3,500 common aberrantly methylated genes, many of which are involved in calcium signaling (Bachmann et al., 2019).

The knockdown of selenoprotein N caused by mutations in the corresponding gene, in addition to myopathy, leads to a deterioration in insulin signaling in skeletal muscle, as indicated by a decrease in Akt phosphorylation and an exaggerated ER stress, which indicates a correlation between a decrease in glucose tolerance of the body, insulin activity and increased ER stress in the muscles (Varone et al., 2019).

It was found that the levels of selenoprotein N (SEPN1) are parallel to oxidoreductin 1 (an enzyme of the family of oxidoreductases) and thioloxidase located in ER. SEPN1 protects the endoplasmic reticulum from peroxides produced by oxidoreductin 1. SEPN1 also enhances the activity of SERCA2 (endoplasmic reticulum pump for calcium imports) by reducing the amount of cysteines in the lumen that are hyperoxidized by peroxides generated by oxidoreductin 1. Cells lacking SEPN1 are hypersensitive to overexpression of oxidoreductin 1 and become defective upon reabsorption of calcium by the endoplasmic reticulum (Marino et al., 2015).

Deletion of SEPN1 alters endoplasmic reticulum uptake of Ca^{2+} , causing an ER stress response, including expression of oxidoreductin (ERO1). The latter transfers the redox potential of ER to a more oxidized state and thereby enhances its effect on Ca^{2+} uptake. The above confirms that SEPN1 is part of the stress-dependent antioxidant ER response and that the CHOP/ERO1 branch of the ER stress response is the new pathogenic mechanism underlying SELENON-related myopathies (Pozzer et al., 2019) (Fig. 1).

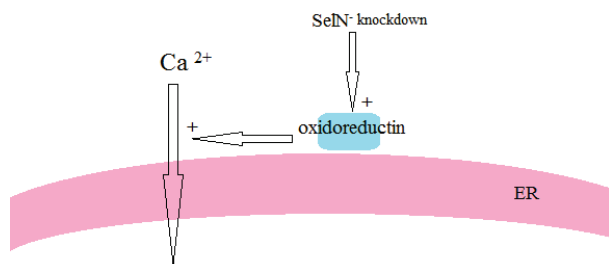


Fig. 1. The signaling pathway is mediated by SelN and oxidoreductin
ER – membrane of endoplasmic reticulum, SelN – selenoprotein N

The model of chicken myoblasts confirms the relationship between selenoprotein K and *gga-let-7f-3p*, namely, selenoprotein K is the target

of *gga-let-7f-3p*. It is revealed there is a direct effect of knockdown and overexpression of *gga-let-7f-3p* on the expression of selenoprotein K. The *gga-let-7f-3p*-selenoprotein K pathway plays a key role in Se deficiency-induced muscle damage through induction of oxidative stress and ERS, which ultimately contributed to apoptosis (Fan et al., 2018).

In an isolated rat heart model, the effect of ischemia/reperfusion on SelT expression lead to increases in the latter. The authors also proposed the use of a derivative of selenoprotein T, SelT43-52, which exhibits a cardioprotective effect after ischemia/reperfusion. Cardioprotection of SelT derivative is accompanied by a significant increase in phosphorylated Akt, Erk-1/2 and Gsk3 α - β and a decrease in p38MAPK. In addition, SelT43-52 inhibits the proapoptotic factors Bax, caspase 3, and cytochrome C and stimulates the antiapoptotic factor Bcl-2. The above indicates the effect of SelT as a modulator of cardiac tissue (Rocca et al., 2018).

An attempt was made to study the effects of SelK in human choriocarcinoma (CCA). The effects of knockdown and overexpression of SelK on the expression of the beta subunit of human chorionic gonadotropin (β -hCG) were studied on a CCA, BeWo, JEG-3, and JAR cell model. It was found that β -hCG levels are regulated and directly proportional to SelK levels. In JEG-3 cell culture, an increase in proliferative, migratory, and invasive abilities was noted in SelK knockdown and a decrease in these activities was observed during SelK overexpression. An interesting fact is that β -hCG affects SelK levels. The aforementioned confirms that β -hCG acts as a promoter of human choriocarcinoma, while SelK appears as a suppressor. The influence of both is via the ERK/p38 MAPK and Akt signaling pathways (Li et al., 2018).

Recent studies have shown that selenoprotein K (SelK), as an ER transmembrane protein, is involved in ER responses to stress and calcium-dependent signal transmissions. SelK in the ER membrane binds to an enzyme protein called DHHC6, resulting in the formation of the SelK/DHHC6 complex, which carries out palmitoylation in target proteins. One of these proteins is the inositol 1,4,5-triphosphate receptor (IP3R), which is responsible for the stabilization of the calcium channel in the ER membrane. SelK-lowering conditions disrupt the calcium flow provided by IP3R. This signaling pathway is involved in the proliferation and activation of immune cells, and has also recently been described in the progression of melanoma (Marciel & Hoffmann, 2019) (Fig. 2).

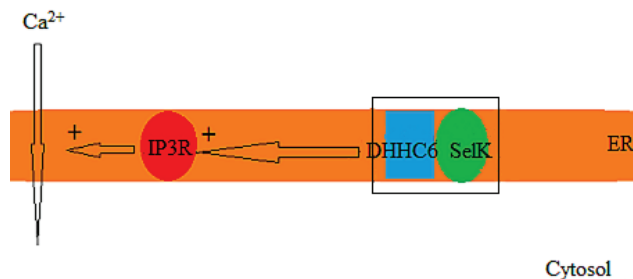


Fig. 2. IP3R signaling pathway and SelK IP3R – inositol triphosphate receptor, DHHC6protein-palmitoyltransferase, SelK – selenoprotein K, ER – endoplasmic reticulum membrane

It was found that SelT is expressed in the membrane of the endoplasmic reticulum in all pituitary cells secreting hormones. Deletion of SelT in corticotropocyte cells promotes the development of a detailed protein response (UPR) and ER stress and reduces protein degradation associated with the endoplasmic reticulum (ERAD) and hormone production (Hamieh et al., 2017).

The function of SelK in the process of the immune response was investigated. Short hairpin RNA was used to suppress SelK expression *in vitro*. Knockdown of SelK decreases the expression of the CHERP protein, the endoplasmic reticulum protein that appears in calcium transport, and also reduces the concentration of free calcium inside the cell. Simultaneously, the expression of the alpha chain of the interleukin-2 receptor (IL-2R α) and the secretion of interleukin-4 (IL-4), which plays key roles in the proliferation and activation of T-lymphocytes, decreases. Selenomethionine excludes the above effects from Sel-

Knockdown and reverses the change in the expression of CHERP and intracellular free calcium (Wang et al., 2017) (Fig. 3).

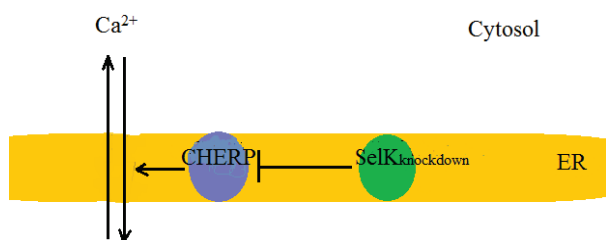


Fig. 3. Ca^{2+} transport regulation by SelK and CHERP protein
CHERP – endoplasmic reticulum protein regulator of calcium homeostasis, SelK – selenoprotein K

The development of melanoma, according to research, requires the expression of selenoprotein K, which is necessary for the Ca^{2+} flux into the cancerous cell. Malignant cells show a strong dependence on the flow of calcium. In the experiment CRISPR/Cas9 was used to form the selenoprotein K deficiency in human melanoma cells. This led to a decrease in the Ca^{2+} flux and impaired function of the specialized receptor (IP3R), which inhibited proliferation, invasion, and cell migration. Consequently, the tumour growth, its metastatic potential depends on the selenoprotein K synthesis in the cancer cell (Marciel et al., 2018).

The effect of selenoprotein N on smooth muscle cells of the myometrium is described. For this, mRNA levels were determined on the mouse model using polymerase chain reaction. Protein was determined by Western blotting. An immunohistochemical analysis of myometrial tissues was also carried out. When selenium is added to the smooth muscle of the uterus the output of Ca^{2+} , Ca^{2+} -calmodulin increases. At the same time, the expression of myosin pulmonary kinase and phosphorylation of the myosin light chain are stimulated, but the amount of reactive oxygen species does not change (Zhou et al., 2018).

A number of authors describe in detail the active interaction of Ero1 α (ER disulfide oxidase promoting tumour progression) with 1,4,5-triphosphate inositol receptors (IP3Rs) or selenoprotein N (SEPN1) with the sarco/endoplasmic Ca^{2+} transport network of ATPase 2 (SERCA2) (Appenzeller-Herzog & Simmen, 2016).

The BGC-823 gastric cancer cell model, which overexpressed SelK and was placed in Matrigel composition, showed a significant decrease in adhesive and migration ability compared to non-SelK expressing cells. By comparing these parameters, overexpression cells and cells with expression of truncated SelK the decrease is not revealed. The same indicators of adhesion and migration have emerged in the culture of embryonic kidney cells HEK-293, which overexpressed SelK. In addition to the above, SelK overexpression causes loss of viability and stimulates apoptosis of cancer cells (BGC-823). At the same time, the level of cytosolic calcium is significantly increased in these cells. However, overexpression of SelK in HEK-293 cells does not reduce viability and does not stimulate apoptosis. Thus, the authors emphasize that SelK reduces the adhesion and migration of cancer cells and at the same time inhibits their viability by inducing apoptosis. Presumably, this effect is through the release of calcium from the endoplasmic reticulum. And only a full-sized protein is capable of exerting such an effect (Ben et al., 2015).

One of the mechanisms of activation of immune cells is associated with an increased flow of calcium from the endoplasmic reticulum into the cytosol, which occurs after the binding of inositol-1,4,5-triphosphate (IP3) to the receptor in the IP3 endoplasmic reticulum (IP3R). The effect of SelK on this chain of signal effects is revealed. Namely, when SelK was knocked down, IP3 generation did not decrease, while IP3R expression was significantly reduced due to violation of palmitoylation of IP3R. Using immunofluorescence and co-immunoprecipitation methods, an interaction is revealed between SelK and the membrane domain of the enzyme responsible for palmitoylation (DHHC6). Knockdown of the latter leads to a decrease in IP3R expression and disruption of the IP3R-dependent Ca^{2+} flux. Thus, the effect of SelK on an important molecular pathway that regulates the function of IP3R and through

this mechanism the flow of calcium, and, accordingly, the activation of immune cells, was discovered (Fredericks et al., 2014).

Signaling pathways mediated by ER lumen selenoproteins (SelF, SelS, SelM)

The interaction of SelS and valosin-containing protein (VCP) of the ER membrane provides the insert of selenoprotein K into the ER membrane. This interaction manages Sel K insertion. It was established that in tissues where selenoprotein S is eliminated, selenoprotein K does not interact with a valosin-containing protein, but the elimination of selenoprotein K does not affect this intercommunism. In turn, ER stress leads to an increase of SelK and Sel S expression (Lee et al., 2015) (Fig. 4).

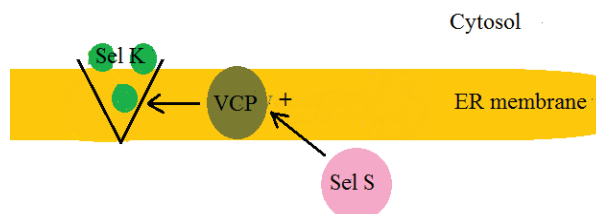


Fig. 4. Regulation of Sel K incorporation through by VCP, and Sel S influence VCP – valosine-containing protein, Sel K – selenoprotein K, SelS – selenoprotein S

The study revealed the effect of selenoprotein M on the proliferation and metastasis of renal cell carcinoma by activating the PI3K/Akt/mTOR pathway, which is one of the main signaling intracellular pathways and provides cell growth, cell proliferation, metabolism and avoidance of apoptosis. Overexpression of selenoprotein M activates this pathway, as well as overexpressed cells reveal an increase in N-cadherin, β -catenin, vimentin, which are known to be positively associated with tumour progression, metastasis and cancer prognosis and are markers of the epithelial-mesenchymal transition (Jiang et al., 2019).

The effect of selenoprotein M on hypothalamic signaling via leptin was studied *in vivo* and *in vitro*. Leptin supports the expression of selenoprotein M in the hypothalamus, however, knockdown of Sel M interrupts the phosphorylation of STAT3 (an intermediary protein that provides a cell response to signals through interleukin and growth factor receptors) with leptin (Fig. 5). *In vitro* it is confirmed on the model of hypothalamic neurons. Conversely, overexpression of Sel M enhances leptin sensitivity. A large number of genes have been revealed in the hypothalamic tissue which is affected by Sel M deficiency, including a protein interacting with thioredoxin, a negative regulator of the TXN system. In general, these data confirm that Sel M is a positive regulator of leptin signaling and TXN antioxidant activity in the hypothalamus (Gong et al., 2019) (Fig. 5).

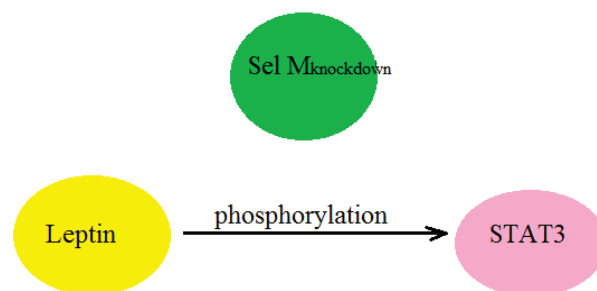


Fig. 5. Regulation of STAT3 phosphorylation by leptin in the hypothalamus STAT3 – a mediator protein that provides cell response to signals transmitted through interleukin receptors and growth factors; Sel M – Selenoprotein M

Using a Hek293 cell model, it was found that overexpression of HSF1 (heat shock factor) and activation of heat shock increases promoter activity and levels of mRNA and SELENOF protein (Selenoprotein F) as well as sodium selenite treatment. This can be regarded as the fact that overexpression and knockdown of HSF1 show the influence of

HSF1 gene transcription regulation on SELENOF and revealed the molecular mechanism of regulation of the SELENOF gene by the HSF1 participation in selenotranscriptome (Ren et al., 2019).

In the cell line 3T3-L1 (preadipocytes) with the SelS gene deletion by imbalance of the most important regulator of apoptosis Bcl-2 (controls the permeability of the mitochondrial membrane), cell death occurs. Knockdown SelS increases the level of IRE1 α protein (a key player that alters gene expression during stress of the endoplasmic reticulum) and p-JNK (activate apoptotic signaling), and also reduces XBP1 (it is a transcription factor that regulates the expression of genes important for the proper functioning of the immune system and cellular response to stress) (Fig. 6). This indicates the SelS modulation of the IRE1 α -XBP1 signaling pathway. The aforementioned suggests that SelS promotes cell survival through the IRE1 α -XBP1 signaling pathway (Men et al., 2018).

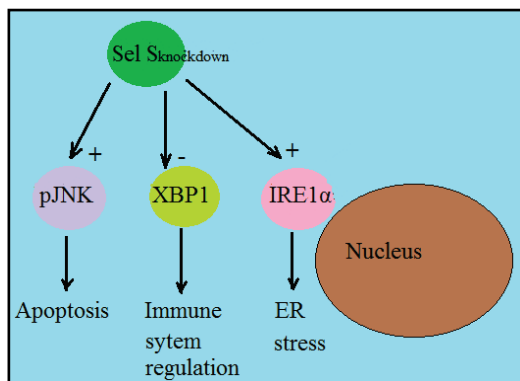


Fig. 6. The influence of SelS in preadipocyte cells on key signaling pathways IRE1 α – inositol transmembrane kinase/endoribonuclease 1 α , a modulator of gene expression; p-JNK – Jun N-terminal kinases, activator of apoptotic signaling; XBP1 – Xbox binding protein, a regulator of genes important for the normal functioning of the immune system

Using the mouse hepatoma model, the effect of reactive oxygen species on apoptosis and necrosis during silencing of selenoprotein S was studied. It was found that knockdown of selenoprotein S damages intracellular calcium homeostasis, stimulates mitochondrial dynamic disorder, ROS accumulation, ATP loss and causes apoptosis and necrosis in cells, however ER stress does not happen. This indicates that SelS silencing initiates apoptosis and necrosis in cells by acting on intracellular calcium homeostasis, and ROS-mPTP-ATP is involved in the transformation of cell death from apoptosis to necrosis to increase damage (Li et al., 2018).

Using a model of cells with and without SelS knockdown, when comparing osteoblastic differentiation and calcification of smooth muscle cells, it was revealed that the lipopolysaccharide activates both classical and alternative nuclear signal transduction pathways- κ B (NF- κ B) during calcification under SelS knockdown conditions. In addition, disabling SelS enhances lipopolysaccharide-induced generation of pro-inflammatory cytokines, expression of TNF- α and interleukin-6. Thus, through inhibition of NF- κ B signaling pathway activity and ER stress SelS can suppress inflammation-induced calcification (Ye et al., 2018).

Selenoprotein M is considered as thiol-disulfide oxidoreductase which provides the formation of disulfide bonds. The last one determines involvement in Ca transfer. A direct relationship is established between the expression levels of selenoprotein M and changes in redox homeostasis. It is stipulated by presence of selenocysteine residue. A strong bond between levels of dietary selenium and selenoprotein M is also determined (Guerriero et al., 2014).

In the model of human kidney embryonic and mouse neuroblastoma cells cultures forcing of ER stress leads to raising of selenoprotein S expression. These events are bound by a mechanism of interaction between membrane protein p97 and selenoprotein (Lee et al., 2014).

In cell culture, ochratoxin induction of cytotoxicity and apoptosis is suppressed by overexpression of selenoprotein S, while the level of glutathione also increases, the number of reactive oxygen species de-

creases, and ochratoxin-induced phosphorylation is inhibited. Knockdown of selenoprotein S has the exact opposite effect: it enhances phosphorylation, increases the number of reactive oxygen species and reduces the level of glutathione (Gan et al., 2017).

Increased expression of selenoprotein S in separate endothelial cells undergoing the impact of tumour necrosis factor (TNF-) leads to the raising of nitric oxide and nitric oxide synthase. TNF-induced adhesion of THP-1 cells to endothelial cells is blocked by excess expression of selenoprotein S and manages such factors of inflammation as interleukin-1, interleukin-6, and interleukin-1. The knockdown of selenoprotein S leads to the opposite effects (Cui et al., 2018).

Selenoprotein F provides monitoring of protein folding and deletion of selenoprotein F RNA suppresses cell proliferation, cell growth. The latter processes restore after the riddance of knockdown factor. Lack of selenoprotein F blocks cells in G1 phase, the ER stress also takes place. Due to selenoprotein F knockdown, adhesive cell junctions shift into the basal part of the cell, which leads to the reduction of invasive and migration abilities. The levels of selenoprotein F determine invertibility of the aforementioned events (Bang et al., 2015).

With an insufficient amount of SelF, an ultramicroscopic examination reveals the appearance of membrane vesicles in them, an increased amount of such endosomes leads to cell shape transformation from spindle to round shape. In this case, actin fibrils are shifted to the periphery and alpha-tubulin overlaps. Rho-associated protein kinase inhibitors inhibit and reverse these changes. Despite the presence of vesicles, cells with deficiency of Sel F are not apoptotic and there is an exact arrangement of F-actin and -tubulin. Thus, selenoprotein F acts as a pathway regulator that counteracts RhoA/ROCK/MLC-dependent nonapoptotic vesicle construction (Bang et al., 2015).

Overexpression of selenoprotein M in mouse hippocampal cells, cerebellar astrocytes and neurons does not ensure the survival of these cells when exposed to hydrogen peroxide, although it reduces the number of reactive oxygen species to a significant extent. Overexpression also leads to a decrease in the influx of calcium into the cells with simultaneous exposure to peroxide, and vice versa, a decrease in the expression of selenoprotein M increases the cytosolic concentration of calcium. Cell death by apoptosis also occurs when the selenoprotein M is completely knocked down, and the number of dead cells is comparable to the number when exposed to hydrogen peroxide on the background of overexpression (Maricclair et al., 2010; Reeves et al., 2010).

Signaling pathways mediated by selenoproteins of the cell nucleus (SelH, SelR or methionine-R-sulfoxide reductase I)

SelH deficiency exacerbates oxidative stress-dependent activation of p53 (a malignant tumour suppressor), where inflammation is a key factor in gastrointestinal oncogenesis in the zebrafish model (Cox et al., 2016). Recently the new nuclear selenoprotein H was described. According to the classification of enzymes, it is recognized as nucleolar oxidoreductase. It is assumed that it manages redox-homeostasis and can prevent some DNA damages (Cox et al., 2016).

It is established that selenoprotein H takes part in both redox regulation and in carcinogenesis. The tumour tissue and undifferentiated tissues in the stomach and intestine epithelium show high expression of selenoprotein H. But a knockdown of selenoprotein H leads to a decrease of cell differentiation, stimulates proliferation and migration. Knockdown of selenoprotein H initiates colonization of tumours and xenografts. Changes in cell cycle include an increase in the rate of all phases. So, selenoprotein H plays the role of cell cycle regulator and control proliferation (Bertz et al., 2018).

Signaling pathways mediated by cytoplasm selenoproteins (SelP, SelW, SelR, SelI)

A regulatory role in the osteogenic differentiation of bone marrow mesenchymal cells has been revealed of a new long non-coding RNA, Bmcob, whose gene is located next to the gene encoding selenoprotein R. The selenoprotein P gene affects the Bmcob regulatory effects. Moreover, some selenoproteins were suppressed by a Bmcob knockdown.

As a result, it was revealed that a new long non-coding RNA affects the protein that binds the sequence of insertion of selenocysteine 2 into selenoproteins, which is a key point in the synthesis of selenoproteins. The authors suggest that Bmcb regulates the expression of a number of selenoproteins, including P selenoprotein, and thereby mediates osteogenesis of bone marrow mesenchymal cells (Sun et al., 2018).

Analysis of gene expression of selenoproteins under the influence of metallic mercury vapour showed a significant increase in the expression of selenoprotein P and GPX1 (glutathione peroxidase 1) (Kuras et al., 2018).

Selenoprotein P is considered by some authors as a diagnostic biomarker and antiproliferative factor in pulmonary arterial hypertension due to the fact that SelP knockout mice exhibit reduced pulmonary hypertension caused by hypoxia. Conversely, mice with increased SelP expression show an increase in pulmonary hypertension provoked by hypoxia. Also, SelP promotes proliferation of PASM (smooth muscle cells of the pulmonary artery) and apoptosis resistance through increased oxidative stress and mitochondrial dysfunction, which were associated with activated hypoxia-induced factor-1 α and metabolic dysfunction glutathione. SelP contributes to the development of pulmonary hypertension, suggesting that it is a new biomarker and therapeutic target for the disorder (Kikuchi et al., 2018).

The effect of SelP on ischemia/reperfusion damage was studied in a mouse model with and without SelP knockout. The infarction zone after reperfusion was significantly smaller in the case of SelP knockout. The TUNEL (method for detecting fragmentation of apoptotic DNA) has revealed a significant decrease in TUNEL-positive nuclei with SelP knockout, which indicates the suppression of apoptosis. At the same time, the level of caspase-3 activation decreased. Evaluation of phosphoinositide-3-kinase/Akt and Erk in knockout mice shows an increase in phosphorylation of these enzymes after ischemia/reperfusion in comparison to wild-type mice, which indicates activation of the transmembrane PI3K/Akt/Erk signal pathway. Overexpression according to the authors leads to an increase in myocardial infarction zone after ischemia/reperfusion in comparison with knockout. Thus, inhibition of SelP has a cardioprotective effect in ischemia/reperfusion via the RISK signaling pathway (Chadani et al., 2018).

In the model of hepatocytes, cell culture glucose injection enhances expression and transcription of selenoprotein P. In the model of human umbilical vein endothelium usually vascular endothelial growth factor (VEGF) stimulates cell proliferation, but the normal amount of selenoprotein P reduces the latter and tubular formation, migration too. Selenoprotein P also suppresses emerging and phosphorylation of reactive oxygen species, which are induced by endothelial growth factor (VEGF). Selenoprotein P inhibits extracellular signaling regulated kinase in the same model. Recovery from injuries is inhibited by expression of selenoprotein P, while knockdown stimulates (Ishikura et al., 2014).

Selenoprotein P, as one of liver secretory proteins is engaged in resistance to insulin. Administration of native selenoprotein P breaks down insulin signals and manages insulin function in both hepatocytes and myocytes. Knockdown and exclusion of selenoprotein P enhance common reactivity to insulin and glucose tolerance in mice. Adenosine monophosphate-activated protein kinase (AMPK) in the last case plays as a mediator in the regulatory activity of selenoprotein P. The aforementioned suppose the use of selenoprotein P as a therapeutic target in diabetes 2 types (Misu et al., 2010).

Deficiency of selenoprotein P shapes a "super-sustainability" phenotype in mice after training and intensifies reactive oxygen species generation, phosphorylation of protein kinase. It also provides activation of the proliferative receptor with peroxide. N-acetylcysteine antioxidant diminishes the production of reactive oxygen species and durability in selenoprotein P deficient mice (Misu et al., 2017).

In a living organism, there is a so-called selenium pool, which is controlled in order to provide vital selenoproteins with the necessary trace element. The central regulatory organ of the pool is the liver, which, in a situation of selenium deficiency, releases SelP into plasma. A special receptor for SelP, 2 apolipoprotein E, expressed in different degrees by tissues, determines the distribution of SelP in the corresponding tissues, being a source of the necessary selenocysteine residue for

them. In the kidneys, N-terminal forms of SelP are filtered, with consequent reabsorption in the proximal convoluted tubules using the megalin receptor (Burk et al., 2015).

Against the background of inflammatory colitis, there is an increase in carcinogenesis during mutations and SelP deficiency in mice. In this case, changes in the pro-tumour microenvironment occur. A decrease in SelP increases the number of so-called M₂-polarized macrophages. Complete removal of SelP in a cancer cell culture increases the number of stem cells among them, indicating an increase in proliferative activity; significantly increases the production of reactive oxygen species and DNA damage. Simultaneously a decrease in cell viability, a change in signal transfer in the WNT signaling pathway caused by oxidative stress is noted (Barrett et al., 2015).

Rat myoblasts were placed in a composition containing mouse selenoprotein P in order to increase the activity of glutathione peroxidase Gpx. It was revealed that shutdown of the apoER2 (a receptor that binds Selenoprotein P and effecting its endocytosis) inhibits Se uptake from (75) Se-labeled Selenoprotein P (Fig.7). Thus, myoblasts absorb Selenoprotein P by apoER2-linked mechanism. At the same time, tissues express apoER2 differently (Kurokawa et al., 2012).

The data on the pathways providing the uptake of SelP by brain neurons are interesting. In the brain, SelP is expressed by astrocytes, the further transport of selenoprotein P through the blood-brain barrier is carried out by binding to LRP2 (lipoprotein-like protein, or megalin), which is a membrane multiligand receptor, Fig. 7) or LRP8 (apolipoprotein with membrane receptor function) (Gong et al., 2018).

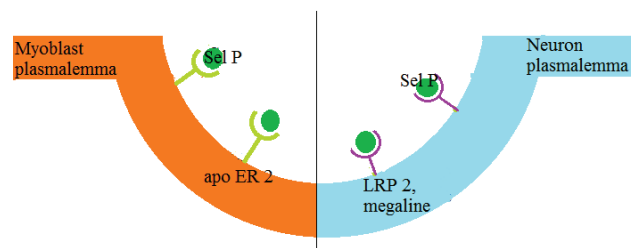


Fig. 7. Transmembrane receptor-mediated transfer of SelP in myoblasts and neurons SelP – selenoprotein P, apoER2 – apolipoprotein E receptor, LRP2 – lipoprotein-related protein receptor or megalin

Four isoforms of selenoprotein P were isolated, while the longest forms bind to the apoER2 receptor, with six or more selenocysteines in the HEK293T cell culture (embryonic renal cells). Moreover, binding occurs with the C-terminal domain of selenoprotein P, the N-terminal domain is not involved in this (Kurokawa et al., 2014).

Since apoER2 is expressed by tissues to varying degrees, but most of all in the brain, it was experimentally confirmed that knockout of selenoprotein P or apoER2 reduces selenium in the brain from about 120 to about 50 ng/g and leads to severe neurodegeneration and death with mild selenium deficiency. It was also found that apoER2 binds selenoprotein P through the blood-brain barrier. In the case of a knockout for selenoprotein P and apoER2, selenium in the brain decreases to 35 ng/g, and severe neurodegeneration develops. Thus, the dual effect of selenoprotein P and apoER2 on the transfer of selenium to neurons is not in doubt. It is apoER2 in the blood-brain barrier that transfers selenium to neurons (Burk et al., 2014).

Thioredoxin reductase-mediated signaling pathways

Participating in many regulatory functions, selenoproteins are controlled by other regulators. For instance, Nrf2, a regulatory protein, affects selenoproteins such as thioredoxin reductase-1 (TrxR1) and glutathione peroxidase-2 (GPx2). Moreover, deficiency of selenium and knockdown of TrxR1 stimulates Nrf2. However, it creates the opposite effect in cancer cells. Hyperproduction of TrxR1 and GPx2 caused by Nrf2 makes cancer cells resistant to chemotherapy, and protects them from oxidative damage. TrxR1 activation has been observed to support the proliferation of cancer cells. The anti-inflammatory activity of GPx2 suppresses the pro-inflammatory effects of the tumour, which also con-

tributes to its development. The effects of Nrf2 also depend on the stage of the cancer (Brigelius-Flohé et al., 2012).

In the case of multiple myeloma, inhibition of Trx1 by sensitized pheochromocytoma cells (PX-12), and TrxR1 with Auranofin disrupts redox homeostasis, which causes apoptosis in myeloma cells and reduces their proliferative activity. Knockdown of Trx1 and TrxR1 also reduces the viability of these cells. When Trx1 is inhibited in cells, resistance to BAY 11-7082, and curcumin, which serve as inhibitors of NF- κ B, one of the key signaling pathways, decreases (Raninga et al., 2015).

Inhibition of TrxR1 reduces hypoxia-induced levels of p65 NF- κ B protein in the nucleus and reduces the expression of NF- κ B-regulated genes in myeloma cells. Thus, inhibition of TrxR1 has an inhibitory effect on the NF- κ B signaling pathway (Raninga et al., 2016).

A study of salivary adenoid cystic carcinoma metastases (SACC) found that TGF- β plays a key role in the epithelial-mesenchymal transition in metastatic SACC. It was revealed that selenium-containing thioredoxin reductase (Trx) affects the TGF- β -induced epithelial-mesenchymal transition. Metastatic SACC revealed significantly increased expression of Trx and N-cadherin and lower expression of E-cadherin compared to non-metastatic SACC tissues. Trx and Akt inhibitors reduced the proliferation and invasion of these cells. As a thioredoxin reductase inhibitor, BBSKE was used. The authors conclude that Trx plays a key role in the invasion and metastasis of SACC through its effect on TGF- β -Akt/GSK-3 β pathway during epithelial-mesenchymal transition (Jiang et al., 2015).

Two metastatic phenotypes (C1 and C6) and two weakly metastatic variants (C4 and C5) were isolated from osteosarcoma. In metastatic types, overexpression of thioredoxin reductase 2 (TXNRD2) is determined, and in the unneoplastic bone tissue, the level of expression of TXNRD2 do not change. Using the thioredoxin reductase 2 inhibitor Auranofin in small doses does not significantly decrease cell viability, while high doses of this inhibitor stimulated ROS-dependent apoptosis (Topkas et al., 2016).

The CT26 mouse colon carcinoma cell model examined the effects of Sep15 and thioredoxin reductase 1 on tumorigenesis. The authors note that the combined deficit of Sep15 and Thx 1 completely changes the anticancer effects that are observed when each of them was suppressed. In Sep15-deficient cells, the γ -interferon-regulated guanine-binding proteins modulating inflammation were significantly reduced, which do not occur with a deficiency of Thx 1. It is interesting that messengers of the Wnt/ β -catenin signaling pathway were increased in cells with a deletion of both Sep15 and Thx1. Thus, the authors conclude that Sep15 and TR1 actively modulate important signaling pathways in colon cancer cells (Tsuji et al., 2015).

A clear connection between thioredoxin reductase 1 and the formation of various tumours, including breast tumours, was determined. Overexpression of thioredoxin reductase 1 (TrxR1) is directly correlated with tumorigenesis. In the model of MCF-10A cells (normal breast cells) exposed to H₂O₂. The prolonged exposure of H₂O₂ to cell culture triggered an increase in TrxR1 expression and activity. At the same time, the cells show high malignancy. The use of an ethaselen inhibitor (BBSKE) partially reversed the epithelial-mesenchymal transition of MCF-10A and MCF-7 cells (mammary adenocarcinoma cells) (Dong et al., 2016).

Breast carcinogenesis is induced in a mouse model using 7,12-dimethylbenzylbenz[a]anthracene in the line of heterozygous deletion of the Trsp gene (thioredoxin reductase) and homozygous line. In mice heterozygous for this trait, the frequency of tumours and survival do not differ. However, in homozygous mice, the incidence of tumours is 54.8% compared to 36.4% in heterozygous mice and survival in homozygous mice is significantly shorter. This confirms that reduced Trsp expression increases susceptibility to carcinogen-stimulated breast tumours (Hudson et al., 2012).

In a model of acute colitis induced by 4% dextran sodium sulfate with selenium deficiency and normal selenium content, the effect of selenoproteins, which play the role of pro-inflammatory elements in colitis, was studied in macrophages. Thioredoxin reductase (Trsp) knockout mice with normal expression showed enhanced colitis and decreased Trsp survival. With the addition of selenium at a dose of 0.4

and 1.0 ppm, the manifestations of colitis decreased and survival increased in both groups. At elevated levels of selenium, increased oxidation of PGE2 (prostaglandin E2) was observed, which is directly related to the Se-dependent activation of 15-hydroxy-PG-dehydrogenase (15-PGDH) in macrophages (Kaushal et al., 2014).

A number of authors describing the thioredoxin reductase system indicate that both cytosolic (TrxR1) and mitochondrial (TrxR2) thioredoxin reductases modulate basic cellular circuits and cellular responses to stress. The results of deletion of enzymes are an increase in lipogenesis, insulin sensitivity, an increase in glycogen stores, aberrant embryogenesis, while an increase in TrxR1 and TrxR2 expression is directly proportional to a decrease in proliferation, an increase in life expectancy and a worsening in the prognosis of cancer. (Dagnell et al., 2018) (Fig. 8).

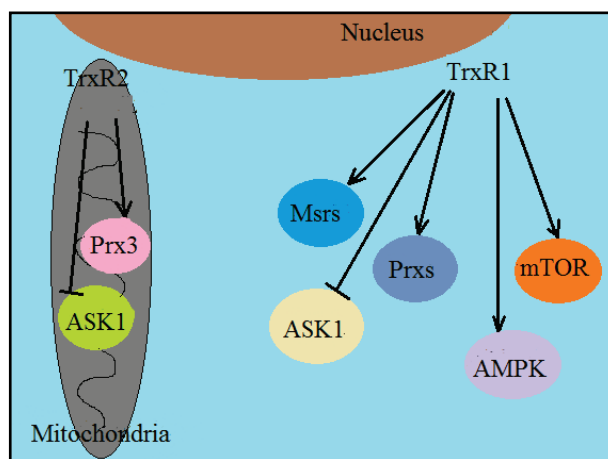


Fig. 8. Intracellular effects of thioredoxin reductases 1 and 2 TrxR1 – cytosolic enzyme; TrxR2 – mitochondrial enzyme; ASK1 – kinase regulating apoptosis signaling; Prx3 – peroxyredoxin 3, an enzyme in the antioxidant system; Msrs – methioninesulfoxid reductase; Prxs – peroxyredoxins; mTOR protein kinase, which is part of the signaling pathway that regulates cell growth and survival; AMPK – cellular protein kinase that controls cell energy balance

The removal of thioredoxin reductase was studied in a model of mice with a breast tumour gene. Sec tRNAs were significantly reduced in breast tissue by more than 70% with any transgene. In other organs, such as the skin and spleen, a decrease in Sec tRNA occurs only in the line of mice with the MMTV-Cre transgene (breast tumour virus). In tissues affected by the tumour process, the expression of specific selenoproteins was different. Moreover, the levels of Sep15 and glutathione peroxidases GPx1 and GPx4 were significantly reduced. Expression of BRCA1 and p53, which are responsible for tumour suppression, also changes. Moreover, these changes occur in MMTV-Cre transgenes to a greater extent. The authors emphasize tissue-specific regulation of selenoprotein expression during deletion of thioredoxin reductase (Kumaraswamy et al., 2003).

Glutathione peroxidase-mediated signaling pathways

In an experiment (DNA hypermethylation is observed in some cancers) with methylation, genes responsible for the expression of glutathione peroxidase 3 (GPX3, selenoprotein) in the cell line of chondrocytes, the effect of oxidative stress was studied. A tendency toward a decrease in expression (GPX3) is revealed in the groups of non-methylation, partial methylation and complete methylation. Also, in the partial and complete methylation groups, the protein level in the PI3K/Akt/c-fos pathway (the pathway responsible for growth, proliferation, and avoidance of apoptosis) increased compared to the non-methylation group (Han et al., 2018).

There is the pathway where the interaction between pro-inflammatory factors occurs, miRNA (plays a regulatory role in post-transcription), SBP2 (selenoprotein-binding protein) and selenoproteins that are associated with oxidation resistance in cartilage. It is found that IL-1 β (pro-inflammatory cytokine) increases hsa-miR-181a-5p and reduces

SBP2 depending on time and dose. At the same time, GPX1 and GPX4 are upgraded. A decreased expression of GPX1 and GPX4 mRNA and expression of SBP2 protein are detected in damaged cartilage but not in smooth cartilage from the same osteoarthritis sample, and vice versa, decreased expression of hsa-miR-181a-5p is also noted (Xue et al., 2018).

Alcohol intoxication causes a depletion of Sel in the liver, which leads to a decrease in the expression and activity of selenium-containing antioxidant enzymes (GPx1, GPx4) and NF-kb, but an increase in the expression of caspase-3. At the same time, a decrease in the activity of pro-inflammatory cytokines and chemokines is noted (Ojeda et al., 2017).

In a colorectal cancer cell culture the effect of GPx2 on the proliferative and migration abilities of cancer cells was studied. Deletion of GPx2 reduces resistance to apoptosis caused by H₂O₂ and significantly reduces proliferative and metastatic abilities. With the elimination of oxygen radical forms, proliferative activity resumes. However, knock-down of GPx2 in cells leads to a loss of their ability to differentiate, and such cancer cells form slowly growing undifferentiated tumours. And vice versa, overexpression of GPx2 leads to tumour differentiation, increases proliferation and growth. The same thing is noted at the usual level of expression. The authors also point to the great potential for early tumour recurrence with overexpression of GPx2. They note that the neutralization of H₂O₂ GPx2 is necessary for the tumour to maintain proliferation, migration capabilities and differentiation (Emmink et al., 2014).

The frequent detection of the methylation of glutathione peroxidase 3 (GPX3) in cancer of the prostate, esophagus, stomach, and breast has prompted the study of this selenoprotein in thyroid cancer. In 46.8 cases, GPX3 is methylated, which correlated with tumour size and metastases to regional lymph nodes. Compared to neighboring tissue samples, where GPX3 expression is not changed, GPX3 expression was either absent or decreased in tumour tissue. The disappearance or decrease in GPX3 expression is associated with hypermethylation of the promoter region. Thus, methylation of the promoter region of GPX3 regulates the expression of this selenoprotein. At the same time, GPX3 suppresses Wnt signaling in cell colonies of papillary thyroid cancer. The authors emphasize that metastasis of thyroid cancer is suppressed by GPX3 by inhibiting Wnt/ β -catenin signaling (Fig. 9) (Zhao et al., 2015).

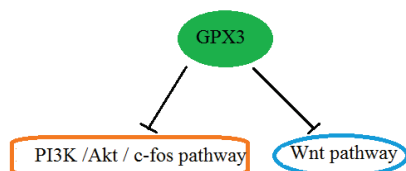


Fig. 9. Inhibitory effect of glutathione peroxidase 3 (GPX3) on Wnt and PI3K/Akt/c-fos signaling pathways Wnt pathway – intracellular signaling pathway, regulating embryonic development, differentiation and malignant development; PI3K/Akt/c-fos pathway – an intracellular signaling pathway regulating the cell cycle, c-fos – protooncogene

It has been reliably established that for many cancers, such as cancer of the prostate, stomach, cervix, thyroid gland and colon, there is a decrease in GPX3 expression and hypermethylation. An experiment on mice with a GPX3 deletion in a colon tumour model reveals an increase in their number but not their size. In the same group of mice, an increase in the degree of dysplasia, an increase in proliferative activity, an increase in the number of pro-tumour macrophages, and an increase in DNA damage are observed. At the same time, activity in the WNT signal transmission chain increases. In a model of Caco2 cells (human adenocarcinoma cells), GPX3 was knocked down, which led to an increase in oxidative stress, an increase in reactive oxygen species, DNA damage, and activation of apoptosis. Summing up, the authors define the function of GPX3 as immunomodulatory (Barrett et al., 2013).

The genetic relationship between the expression of selenoproteins and the risk of breast cancer has been studied using polymorphisms in the genes SEPP1 (selenoprotein P), GPX1 (glutathione peroxidase 1), GPX4 (glutathione peroxidase 4) and antioxidant enzyme genes SOD2. The risk of breast cancer was reduced by 60% in women homozygous for SEPP1. At the same time, Leu carriers for GPX1 polymorphism had teratogenic risks two times higher. It was also found that the activity of

GPX in red blood cells depends on the genotype, and this activity is lower in women with the development of breast cancer at a later age. The MCF7 cell model (invasive breast adenocarcinoma cells) also shows an increase in GPX1 levels when exposed to β -estradiol and sodium selenite (Méplán et al., 2013).

A dual effect of glutathione peroxidase 2 (GPx2) on colon carcinogenesis has been identified. On a GPx2 knockout mouse model and in the minimized, moderate, and increased selenium intake, treatment with an oncogen (azoxymethane) was performed. Interestingly, minimized and increased selenium intake in GPx2 knockout mice shows a significant decrease in the number of tumours compared to the wild type. The authors suggest that GPx2 knockout initiates apoptotic death of damaged and precancerous cells, as the GPx2 is significantly increased and suppresses apoptosis of atypical cells in dysplastic crypts of wild-type mice. In the intestinal mucosa with moderate consumption of selenium, the number of tumours in both genotypic groups is the same, but the tumour size is larger in mice with knockdown, where an inflammatory processes increase. Thus, the role of GPx2 as a modulator depends on the presence of the inflammatory process and the level of selenium consumption (Müller et al., 2013).

The role of glutathione peroxidase 2 (GPX2) in humans and rats has been investigated in a castration-resistant prostate cancer model. It was revealed that deletion of GPX2 caused a significant suppression of growth and an increase in the number of reactive oxygen species in rat and human adenocarcinoma cells. According to the author, suppression of proliferation in knockout mice is associated with cyclin B1-dependent G2/M blockade (Fig.10). Also knockdown of glutathione peroxidase 2 (GPX2) inhibits tumour growth. Immunohistochemistry reveals GPX2 expression is significantly higher in the focus of residual cancer after hormone therapy than in focus of cancer without it. Significantly lower survival is observed in patients with high expression of GPX2 in biopsy than in patients with low expression or its complete absence. The authors conclude that GPX2 significantly affects the proliferation of prostate cancer through protection against signal transduction of reactive oxygen species and can act as a prognostic marker (Naiki et al., 2014) (Fig. 10).

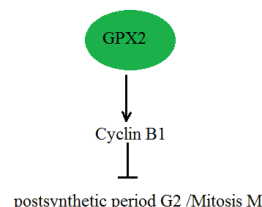


Fig. 10. Inhibition of proliferative processes by glutathione peroxidase 2 (GPX2) mediated by cyclin B1

In some tumours, the glutathione peroxidase 3 (GPX3) gene is methylated, which is studied in colorectal carcinoma using models of the primary tumour, cell lines, knockdown cell lines, and xenograft tumour cell lines. Methylation of the glutathione peroxidase 3 gene leads to a decrease in the expression of this enzyme and an increase in sensitivity to cisplatin. And conversely, increased expression or the ability to increase expression reduces sensitivity to cisplatin. In the GPX3 knockdown model of a cell line, survival of cells is not possible due to a redox balance violation. Methylation of the GPX3 promoter in the tumour xenograft model also reduces the expression of the enzyme and increases sensitivity to cisplatin with reverse tumour development in the case of knockdown and continued growth in the case of the wild type (Pelosof et al., 2017).

Redox signaling regulates physiological self-renewal, proliferation, migration, and differentiation in the gastrointestinal epithelium by modulating Wnt/ β -catenin and Notch signaling pathways mainly through NADPH oxidases (NOXs). The progression of inflammatory bowel disease depends on the balance of pro-inflammatory redox-sensitive pathways, such as NLRP3 inflammation and NF- κ B, and adaptive activation of Mn superoxide dismutase and glutathione peroxidase 2. In colorectal cancer, redox signaling has two opposite sides: on the one hand, NOX1 activation and the H₂O₂ derivative enhance Wnt/ β -catenin and

Notch proliferation pathways; on the other hand, reactive oxygen species inhibit tumour progression through activation of apoptotic mechanisms (Pérez et al., 2017).

Knockdown of glutathione peroxidase 4 gene in the mouse epidermis leads to hyperplasia, inflammatory infiltrates in the dermis, and alopecia immediately after birth, however, after 5 weeks, the disorder disappears. In keratinocyte cell culture, the knockdown of GPx4 reduces cell adhesion and increases lipid peroxidation and cyclooxygenase-2 levels, which indicates the effect of GPx4 in the skin on the regulation of cyclooxygenase-2 morphogenesis (Sengupta et al., 2013).

Overexpression of GPX2 is noted in the cell lines of UC, BC31, and RT4 bladder carcinoma. Deletion of GPX2 inhibits the formation of reactive oxygen species in these cells, inhibits their growth and activates apoptosis through stimulation of caspases 3 and 7 (Naiki et al., 2018).

GPx3 directly interacts with the p53-induced gene, and overexpression of GPx3 in prostate cancer cell lines stimulates the death of apoptotic cells, which was probably due to an increase in the number of reactive oxygen species and activation of caspase 3. It was also found that apoptosis due to ultraviolet light is mediated by signal transmission in the way of the GPx3-p53 (Wang et al., 2012).

Increased expression of Nrf-2 in glioma stem cells increases transcription of GPx1 and reduces the formation of reactive oxygen species, which leads to radioresistance of glioma. MicroRNA (miR)-153, the gene of which is associated with Nrf-2, was suppressed with an increase in Nrf-2. And vice versa, overexpression of miRNA-153 miRNA reduced the ability of glioma stem cells to form neurospheres, stimulated differentiation through ROS-mediated activation of p38 MAPK. Thus, overexpression of miR-153 reduced the radioresistance and stemming of glioma cells by targeting the Nrf-2/GPx1/ROS pathway (Yang et al., 2015).

Overexpression and knockdown of GPX4 are able to modulate the lethality of 12 inducers of ferroptosis. The most sensitive to GPX4-regulated ferroptosis were renal cell carcinoma and B-cell lymphomas (Yang et al., 2014).

The heat shock protein HSPA5 negatively affects ferroptosis in pancreatic duct carcinoma cell models. When transcription factor 4 is activated, HSPA5 expression is stimulated, which in turn leads to GPX4 binding and protection against lipid peroxidation. Thus, the HSPA5-GPX4 pathway targets resistance to ferroptosis (Zhu et al., 2017).

Deletion of one or both GPx3 alleles leads to an increase in the incidence of prostate cancer in a mouse model and is mediated by activation of the Wnt/ β -catenin signaling pathway (Chang et al., 2016).

Signaling paths mediated by diiodinases

Iodothyronediiodinases or simply diiodinases, enzymes containing selenocysteine, which refers them to the family of selenoproteins, catalyze the activation of T_4 by converting it into T_3 , while the iodine atom is removed from the inner or outer ring of the hormone. Moreover, selenocysteine is located in the active centers of enzymes (Schweizer et al., 2014). Deiodinase 3 (DIO3) is significantly activated with papillary thyroid carcinoma, with a direct correlation between an increase in DIO3 level and tumour size, metastasis. Using the model of thyroid papillary carcinoma cells (K1 and TPC-1), the signaling pathways involved in DIO3 activation in this tumour are studied. Reduced DIO3 expression in cells in K1 and TPC-1 specifically inhibits BRAF, MEK, or p38 oncogen signaling. siRNA-mediated deletion of DIO3 stimulates a decrease in the expression of cyclin D1 and a partial arrest of the cell cycle of the G1 phase, thereby inhibiting cell proliferation. At the same time, blocking the Hedgehog signaling pathway (SHH) leads to a significant decrease in DIO3 mRNA. The authors indicate that activation of the MAPK and SHH signaling pathways alters the levels of DIO3 expression in papillary thyroid carcinoma. Moreover, the deletion of DIO3 reduces the proliferation and growth of the tumour (Romitti et al., 2016) (Fig. 11).

Signaling pathways mediated by methionine sulfoxide reductase

MsrA, which belongs to the class of thiol oxidoreductases containing catalytic cysteine (Cys) or selenocysteine (Sec) residues, mediates

ubiquitination of the 14-3-3 zeta protein and promotes the binding of 14-3-3 proteins to alpha synuclein in the brain. MsrA in mammals can compete for the capture of ubiquitin using the same active site that is contained for binding methionine sulfoxide and mice knocked out by MsrA have elevated levels of dopamine expression (Deng et al., 2018).

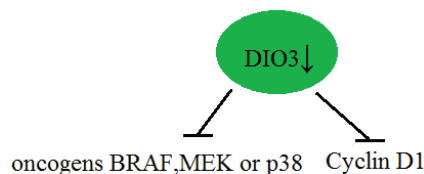


Fig. 11. Inhibition of signaling translation BRAF, MEK, p38 oncogenes, and cyclin D1 expression by deiodinase 3 DIO3 – deiodinase 3, a BRAF – protooncogene that influences normal cell growth and differentiation and participates in the MAPK/ERK signaling pathway; MEK – mitogen-activated protein kinase; p38 – protein kinase of the MAPK signaling pathway

Selenoprotein methionine R-sulfoxide reductase B1 (MsrB1) controls actin assembly along with Mical proteins through stereospecific oxidation and methionine reduction in a reversible, site-specific manner. MsrB1, an antagonist of the Mical protein, which converts two methionine residues in actin into methionine-R-sulfoxide, reduces the last one to methionine, which ensures disassembly and assembly at the same time. Stimulation of the expression of MsrB1 by macrophages reveals before their activation (Gladyshev et al., 2014).

The selenoprotein-containing methionine sulfoxide reductase Msr is studied in stellate cells of the pancreas. It was found that rat stellate pancreatic cells express MsrA, B1, B2, their expression is reduced in cell culture. Overexpression of these selenoproteins enhances ATP-dependent increase in calcium, but at the same time reduces the formation of reactive oxygen species and the production of IL-1, which are caused by lipopolysaccharides. Overexpression of MsrA, B1 also suppresses the dominance of acinar cells over stellate cells during their joint cultivation, which indicates the important role of Msr in the development of stellate pancreaticocytes (Liu & Cui, 2019).

In vitro knockdown of methionine sulfoxide reductase B1 (MsrB1) inhibits hepatocellular carcinoma cell growth, while MsrB1 interference enhances apoptosis, which is caused by hydroperoxides. At the same time, silencing MsrB1 inhibits the phosphorylation of ERK, MEK, and p53 proteins (key players in the MAPK signaling pathway) while increasing PARP and caspase 3, which causes mitochondrial damage. *In vivo* silencing of MsrB1 actively inhibits tumour growth. Moreover, knockdown reduces the migration and invasion of hepatocellular carcinoma cells by suppressing the epithelial-mesenchymal transition (EMT). Thus, the authors emphasize that MsrB1 regulates the proliferation and migration of hepatocellular carcinoma cells by modulating the pathways of MAPK and EMT (He et al., 2018) (Fig. 12).

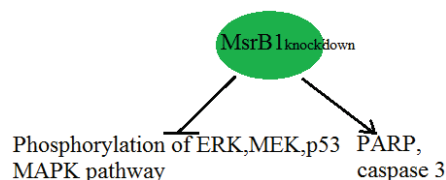


Fig. 12. Inhibition of protein phosphorylation of the MAPK signaling pathway and increase of PARP and caspase by methionine sulfoxide reductase B1 MsrB1 – methionine sulfoxide reductase B1; ERK – extracellular signal-regulating kinase; MEK – mitogen-activated extracellular kinase; p53 – protein involved in transcription and regulation of the cell cycle; PARP – enzymes that regulate post translational modifications of proteins; a caspase3 – proteolytic enzyme whose activation is involved in cell apoptosis

In a model of mice knocked out with the selenium-containing methionine sulfoxide reductase MsrA gene, a study of the effect of the last one on inflammatory reactions induced by lipopolysaccharide (LPS) reveals a high susceptibility of mice to LPS-induced lethal shock. An in-

crease in serum cytokines IL-6 and TNF- α was also noted. Initial and LPS-induced levels of reactive oxygen species were elevated, as were the levels of phosphorylation of p38, JNK, and ERK, indicating activation of MAPK. In addition, NF- κ B expression (a transcription factor that controls the expression of immune response, apoptosis, and cell cycle genes) is increased. The authors suggest that MsrA deficiency negatively regulates pro-inflammatory responses by inhibiting ROS-MAPK-NF- κ B signaling pathways (Singh et al., 2017) (Fig. 13).

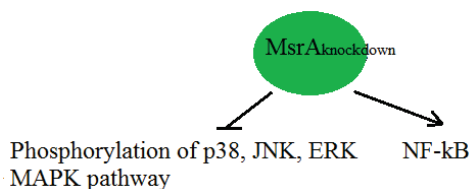


Fig. 13. Inhibition of protein phosphorylation of the MAPK signaling pathway and increase of NF- κ B by methionine sulfoxide reductase A

ERK – extracellular signal-regulating kinase; MsrA – methionine sulfoxide reductase A; JNK – Jun N-terminal kinases, activator of apoptotic signaling; p38 – protein kinase of the MAPK signaling pathway; NF- κ B – transcription factor, regulator of expression of immune response genes, apoptosis and cellular response

Fan et al. (2015) regards MsrA as a factor limiting uncontrolled neuroinflammation, since MsrA expression increased upon microglia activation. Under the influence of MsrA, inflammation is reduced, which was provoked by lipopolysaccharide (LPS). Inhibition of inflammation occurs by inhibiting signaling pathways such as mitogen-activated p38 and ERK protein kinases (MAPKs) and nuclear factor kappaB (NF- κ B). This confirms the direct involvement of MsrA in neuroinflammation mediated by microglia.

Also Lee et al. (2017) in a mouse model determine that selenium-containing MsrB1 exhibits increase expression in activated macrophages and is thus involved in the body's immune responses. It is noted that MsrB1 is activated by lipopolysaccharide (LPS), while the other enzymes of the Msr family remain intact. Deletion of the MsrB1 gene does not interfere in macrophages with the functioning of the signaling pathway that was started by LPS, but causes a decrease in the generation of anti-inflammatory cytokines such as interleukin (IL)-10 and the receptor antagonist IL-1. This is due to the fact the production of pro-inflammatory cytokines increase significantly. It follows that MsrB1 controls immune responses by stimulating the expression of anti-inflammatory cytokines in macrophages.

In the cell culture of the lens epithelium, the selenoprotein R knockdown with the accompaniment of galactose-induced apoptosis show stimulation of oxidative stress. The influence of galactose in the case of selenoprotein R knockdown leads to a more powerful rise in glucose-regulated protein levels and decreases mitochondrial membrane potential due to the release of mitochondrial cytochrome. Simultaneously the number of apoptotic cells rises (Dai et al., 2016).

The deficiency of MsrB3 (methionine sulfoxide reductase B3) facilitates tumour cells apoptosis by the mitochondrial pathway, which leads to destruction of tumour cells. ER stress causes these changes. The proapoptotic Bim molecule is activated by MsrB3 starvation and initiates ER-stress induced apoptosis. Cytosolic levels of Ca²⁺ are increased due to ER stress in the case of MsrB3 deletion (Kwak & Kim, 2017).

In the model of cardiovascular diseases, the role and signaling pathways of methionine sulfoxide reductase A (MsrA), which is determined in all layers of the vascular wall of human arteries and mice, were determined. The deletion of the MsrA gene in mice does not affect the area of experimental atherosclerotic damage and damage after thrombosis, but after ligation of the carotid artery, the area of regeneration of damaged arteries is significantly larger in MsrA-deficient mice. Also, in the case of MsrA deficiency in aortic smooth muscle cells, proliferation accelerates due to the accelerated G1/S transition, and the generation and activity of the cyclin D1 protein and cdk4/cyclin D1 complex increase, which in turn leads to increased phosphorylation of retinoblastoma protein and transcription E2F. MsrA deficient cells also show a

significant increase in 1/2 kinase, indicating an increase in the activity of the Ras/Raf/mitogen-activated protein kinase signaling pathway (Klutho et al., 2015).

Methionine sulfoxide reductase B1 (MsrB1), being one of the enzymes that inactivate methionine sulfoxides, which are formed from reactive oxygen species, has been studied in some tumours. The knockdown of this selenoprotein inhibits the proliferation of u2os cells (an osteosarcoma cell line) and also affects the pathway of mitogen-activated protein kinase (MAPK) by suppressing phosphorylation of Erk, MeK and p53 expression in u2os cells. In the case of a xenograft of a similar tumour in mice, knockdown B1 (MsrB1) perfectly inhibits the growth of the neoplasm, and also significantly reduces the migration and invasion of u2os cells. Also MsrB1 controls the epithelial-mesenchymal transition by affecting the cytoskeleton by increasing the expression of E-cadherin and decreasing N-TGF- β 1, fibronectin, vimentin, c-myc, and β -catenin. Thus, the authors emphasize that the MsrB1 gene can serve as a target against tumours (Li et al., 2018).

Signal pathways of selenoproteins without specific localization

Knockdown of selenoprotein U in the testicle cells of the chicken model causes an increase in mRNA and expression of autophagy and antiapoptosis proteins while reducing antiautophagic (mTOR) and proapoptotic proteins. Inactivation upon knockdown of selenoprotein in mTOR, which is a component of the signaling pathway that regulates basic cell processes, such as growth, proliferation, indicates the regulatory effect of this selenoprotein on such an important regulation mechanism. At the same time, knockdown of selenoprotein U causes a decrease in the activity and expression of such participants of the intracellular signaling pathway as phosphoinositide-3-kinase (PI3K) and protein kinase B (PKB/Akt) both at the mRNA level and at the protein level (Sattar et al., 2018) (Fig. 14).

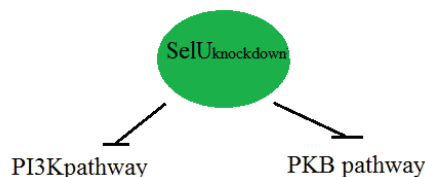


Fig. 14. Inhibition of PI3K and PKB signaling pathways by knockdown of selenoprotein U Sel U – selenoprotein U; PI3K – phosphoinositide-3-kinase; PKB – protein kinase

Researchers suggest that *in vivo* use of apomorphine in lung adenocarcinoma prevents brain metastases by affecting the KIF16B (protein whose biological functions are associated with transport, alternative splicing), SEPW1 (selenoprotein W) and TESK2 associated with premetastasis. Patients with poor survival have a low expression of these genes, which can affect the cellular and molecular dynamics of premetastasis (Singh et al., 2018).

In the chicken model, the inflammatory process and selenoprotein W were studied. Lymphoid tissue and cultivated spleen leucocytes were used for the study effects of selenoprotein W. Diet deficiency of selenium impacts on and diminishes selenoprotein W mRNA expression, which in turn stimulates increase in parameters of COX-2 (cyclooxygenase-2), iNOS (nitric oxide synthase), NF- κ B (nuclear factor- κ B), PTGE and TNF- α (tumour necrosis factor). Selenoprotein W deletion leads to damage to lymphoid tissue (Yu et al., 2015).

In the model of lung lymphocytes with selenoprotein W deletion, which are exposed in H₂O₂, the impact on cell apoptosis, viability, and expression of mRNA of selenoprotein W is revealed. Deletion of selenoprotein W leads to diminishing of cell vitality, speeding of apoptosis and increases sensitivity to H₂O₂. The cell treatment with sodium selenite strongly enhance selenoprotein W expression, and cell apoptosis caused by H₂O₂ decreases, cell vitality increases (Yu et al., 2014).

One of the less studied selenoproteins O impacts on chondrocyte differentiation: it is revealed mRNA and selenoprotein O rise during chondrogenic induction of ATDC5 cells. Knockdown of selenoprotein O leads to a reduction of chondrogenic differentiation accompanied by

some cartilaginous glycosaminoglycans cumulation and a decrease of alkaline phosphatase activity in cells with Selene deficiency. The suppression of proliferation is caused by cell cycle progression delay. Deletion of selenoprotein O induces chondrocytes death by apoptosis (Yan et al., 2016).

Conclusions

The participation of selenoproteins in many signaling pathways confirms their modulating role in many pathogenetic processes. When analyzing the authors' data, the following molecular signaling pathways in which the influence of selenoproteins are involved are distinguished:

- PI3K/Akt/Erk;
- PI3K/Akt/mTOR – main signaling intracellular pathway, providing growth, cell proliferation, metabolism and avoidance of apoptosis;
- PI3K/Akt/c-fos – pathway responsible for growth, proliferation, avoidance of apoptosis;
- IRE1 α – sXBP1 – pJNK – the first participant in the signaling pathway changes gene expression during stress of the endoplasmic reticulum; the second is a transcription factor that regulates the expression of genes important for the proper functioning of the immune system and the cellular response to stress; and the third activate apoptotic signaling;
- NF- κ B transcription factor controlling the expression of the immune response, apoptosis, and cell cycle genes;
- TGF- β -Akt / GSK-3 β ;
- Wnt/ β -catenin – intracellular signaling method, regulating embryonic development;
- MAPK;
- PKB/Akt.

For example, some of them are closely related to the regulation of Ca²⁺ flux both inside the cell and across the membrane of the endoplasmic reticulum. Modulation of the Ca²⁺ flow is the basis of such pathological processes as myopathy, carcinogenesis.

Changes in the Ca²⁺ flow through the endoplasmic reticulum can be modulated by SelN and SelK, the activity of the last one being associated with the inositol triphosphate receptor (IP3R), which is the Ca²⁺ channel. The impact on this molecular pathway is carried out indirectly through special proteins (DHHC6, CHERP).

Signaling pathways that regulate many basic functions such as growth, cell proliferation, metabolism, initiation of apoptosis, and response to stress are interrelated with selenoproteins. So SelS modulates the signaling pathway IRE1 α – sXBP1 – pJNK, SelM is connected with the signaling path PI3K/Akt/mTOR. SelP, which has a special apoER2 receptor in the endoplasmic membrane, also influences the PI3K/Akt/Erk signaling pathway.

Thioredoxin reductases 1 and 2, cytosolic and mitochondrial, respectively, are noted in the regulation of such intracellular promoters as ASK1 – kinase, Prx3 – peroxyredoxine 3, Msrs – methioninsulfoxidoreductase, and mTOR – protein-kinase important mechanisms and, therefore, are active in molecular mechanisms.

Three isoforms of glutathione peroxidase are promoters of some signaling pathways, of which GPX3 is related to the PI3K/Akt/c-fos and Wnt/ β -catenin signaling pathways, GPX1 and GPX4 are associated with the NF- κ B caspase signaling pathway, and GPX2 realizes its effect through cyclin B1 per cell cycle.

Among the isoforms of deiodinases, deiodinase 3 (DIO3), which is associated with the MAPK and SHH signaling pathways, is mentioned; activation of the latter one leads to a change in the expression levels of this selenoprotein. Methionine sulfoxide reductases are also interconnected with some signaling pathways.

In addition to the above signaling pathways, many selenoproteins directly affect other regulatory proteins, such as p53, which is a suppressor of the formation of malignant tumours (SelH), oxidoreductin, p 38, protein kinase of the MAPK signaling pathway.

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