SCIENTIFIC REVIEWS AND LECTURES

DOI 10.25789/YMJ.2023.83.24

УДК 612.014

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# MODERN CONCEPTS OF APOPTOSIS

The review is devoted to the generalization of modern knowledge about such a type of cell death as apoptosis. To date, it is known that apoptosis is not just a programmed cell death that ensures the elimination of old cells with minimal damage to surrounding tissues, but it is also a complex mechanism that can promote survival and proliferation, as well as induce and suppress the inflammatory process. Drugs that cause enhanced apoptosis are being actively studied for the treatment of oncological diseases. The mechanisms of cell death selection are still being studied, but it is already known that weak effects on the macroorganism promote the activation of apoptosis and autophagy, while stronger effects promote necrosis. Low levels of apoptosis contribute to the accumulation of damaged cells, aging, and genome instability. Reduced accumulation of senescent cells improves homeostasis and lifespan.

**Keywords:** apoptosis, apoptotic bodies, caspases.

The review is devoted to the generalization of modern knowledge about such a type of cell death as apoptosis. To date, it is known that apoptosis is not just a programmed cell death that ensures the elimination of old cells with minimal damage to surrounding tissues, but it is also a complex mechanism that can promote survival and proliferation, as well as induce and suppress the inflammatory process. Drugs that cause enhanced apoptosis are being actively studied for the treatment of oncological diseases. Another function of apoptotic bodies has been revealed - the delivery of nutrients to cells. The mechanisms of cell death selection are still being studied, but it is already known that weak effects on the macroorganism promote the activation of apoptosis and autophagy, while stronger effects promote necrosis.

Depending on the cell type, a decrease in temperature can lead to both stimulation and inhibition of the apoptosis process. For most cells, induction of apoptosis is obviously a typical response to cooling and subsequent return to physiological temperature. At the same time, blockade of opiate receptors during prolonged cold exposure (-4 C 4 hours / 7 days) reduces the percentage of apoptosis of lymphocytes.

It has been proven that exposure to heavy metals inhibits cell death through apoptosis and initiates the activation of necrosis. Although apoptosis is a defensive response to pathogen entry, some microorganisms, such as Staphylococcus aureus, can inhibit apoptosis, and some viruses have learned to model apoptosis in such a way as to support replication.

Various substances and preparations can exert their influence on the intensity of cell death. The ability of β-glucans to stimulate apoptotic pathways or proteins involved in apoptosis opens up a new area in cancer therapy. With unregulated apoptosis, the appearance of diseases associated with premature aging is likely. All molecular mechanisms of aging can regulate programmed cell death through apoptosis. Low levels of apoptosis promote accumulation of damaged cells, aging, and genomic instability, but in response to injury/damage, low levels of apoptosis prevent tissue destruction and promote cell survival, proliferation, damage repair, and regeneration. Reduced accumulation of senescent cells improves homeostasis and lifespan.

**Introduction.** Apoptosis is a genetically programmed cell death that occurs regularly to maintain a homeostatic balance between the rate of cell formation and cell death. Disruption of this balance can contribute to abnormal cell growth or proliferation, as well as cancer and autoimmune pathologies. It is believed that apoptosis is crucial in terms of embryo development throughout the growth of the organism, promoting tissue renewal, as well as getting rid of inflammatory cells [35,22]. Apoptosis is characterized by morphological changes in the cell structure, as well as a number of enzyme-dependent biochemical processes. As a result of apoptosis, cells are removed from the body with minimal damage to surrounding tissues [31,5].

The complexity of apoptosis has been the focus of a number of studies that have accumulated a vast amount of knowledge that has led not only to a better understanding of the fundamental process, but also to the creation of effective treatments for diseases. Drugs and therapeutic measures based on the current understanding of apoptosis have been used for a long time. Small molecule apoptosis inducers have been clinically used to kill abnormal cells and hence treat diseases such as cancer. Biological agents with improved apoptotic efficiency and selectivity, such as recombinant proteins and antibodies, are under active investigation. Apoptosis also produces membrane-bound vesicles resulting from the disassembly of apoptotic cells, now known as apoptotic bodies (ApoBDs). These small sealed sacs containing information as well as substances from dying cells were previously considered as a container for the disposal of a dead cell, until it was found that they were able to deliver useful materials to healthy recipient cells (for example, autoantigens) [37].

To detect signs of apoptosis in the study of cellular metabolism, there are several methods that are often used to detect DNA fragmentation as one of the most specific results of apoptosis. To date, three routine assays have been developed, differing in their principles for detecting DNA fragmentation. DNA ladder analysis reveals a characteristic "DNA ladder" pattern formed during internucleosomal DNA cleavage. The Nick-End Labeling Terminal Deoxynucleotide Labeling (TUNEL) assay detects DNA strand breaks using a terminal deoxynucleotidyl transferase that catalyzes the addition of modified deoxynucleotides to DNA strand breaks. The Comet assay can be used to detect nuclear decay resulting in single-/double-stranded DNA breaks [33].

The mechanisms that determine the choice of the path of cell death are not completely clear, but the stronger the impact, the stronger the response in

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the form of cell necrosis, a powerful inflammatory and immune response of the macroorganism. Weak effects cause an intensification of autophagy and cell apoptosis without obvious inflammatory and immune responses. The death of macroorganism cells (humans, animals), due to external or internal causes, causes an immune response to damage. At the same time, microbial effects are always dosed by the concentration and viability of the pathogen, its soluble products, and localization of the lesion [3].

The interplay between autophagy and apoptosis affects several pathologies, including multiple rheumatic diseases. Because mitochondria are important regulators in maintaining cartilage homeostasis, mitochondrial turnover through mitochondrial biogenesis and mitochondrial degradation may play an important role in the pathogenesis of osteoarthritis (OA). Scientists discuss the role of mitochondrial dysfunction in the pathogenesis of OA, identifying the peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC1α) as a potent regulator. Dysregulation of the balance between autophagy and apoptosis may be involved in the pathogenesis of rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome. Indeed, it may regulate immune cell survival, peptide citrullination, self antigen presentation, and B and T cell maturation. Notably, several currently used disease-modifying antirheumatic drugs (DMARDs), including glucocorticoids, hydroxychloroquine, rapamycin, anti-TNFα, and Jak inhibitors, may act via autophagy/apoptosis pathways [25].

It is increasingly recognized that apoptosis is more than just cell elimination. It plays an important role in cellular communication with the microenvironment. These interactions with surrounding cells can have different and sometimes opposite results. Apoptotic cells can promote survival, proliferation, and inflammation, but can also prevent inflammation [32].

Thus, the modulation of programmed cell death has great therapeutic potential in a wide range of diseases, including infectious, neurodegenerative, autoinflammatory and metabolic diseases, and cancer. However, the manipulation of cell death and inflammation for therapeutic intervention is a delicate process, highly specific to the context of the disease of interest, making the selection of the appropriate target molecule critical [8, 12, 16].

**1. Effect of cooling on apoptosis.** Many works are devoted to the study of the mechanisms of cell death under various conditions. For example, the authors of [9] studied the effect of apoptosis on cell damage when the body temperature drops below 37°C. It was found that both proapoptotic and antiapoptotic processes are triggered during hypothermic exposure of cells. With a slight cooling, caspases take part in the processes of apoptosis, initiating the breakdown of anti-apoptotic proteins of the Bcl-2 family and proteolysis of the DNase inhibitor responsible for DNA fragmentation. It was found that RNA-binding protein (cold-inducible RNA-binding protein), which can inhibit the process of apoptosis caused by oxidative stress, is of great importance for the mechanisms of cold adaptation. Depending on the cell type, a decrease in temperature can lead to both stimulation and inhibition of the apoptosis process. For most cells, induction of apoptosis is obviously a typical response to cooling and subsequent return to physiological temperature. However, in some types of cell cultures, as well as in cells of cold-adapted animals, at a temperature below physiological, the content of proapoptotic factors does not increase, but, on the contrary, apoptosis is inhibited or the cell cycle stops in the “hibernation” (G0) phase. Studies have shown that apoptosis induced by hypothermia and subsequent warming of cells develops along an internal (mitochondrial) rather than external (receptor-dependent) pathway. The background for this is a higher content of IL-10 in the blood at low concentrations of IL-1. One of the causes of cell damage during hypothermic exposure may be oxidative stress, which is the result of an increase in the amount of hydroxyl radicals and other reactive oxygen species [9, 13].

Endogenous opioid peptides released during stress are involved in the regulation of lymphocyte apoptosis. It has been shown that blockade of opiate receptors during prolonged cold exposure (-4 C 4 hours / 7 days) reduces the percentage of lymphocyte apoptosis, while acute cold stress, regardless of the blockade of opiate receptors, enhances apoptosis of CD8 cells [13].

Stress is one of the factors contributing to the development and aggravating the course of diseases. According to the results of studies conducted on outbred rats, which were placed in a refrigerator, immunocompetent peripheral blood cells change their activity under the influence of cold exposure. Under cold stress in male and female mice, the absolute and relative content of T-regulatory lymphocytes in the peripheral blood decreased and the relative content of activated T-helpers increased, and the volume fraction of clear centers of lymphoid nodules in the spleen decreased. A number of differences were also revealed between males and females of the control groups: in the peripheral blood, males had a higher number of platelets and an absolute number of T-regulatory lymphocytes and a lower content of cytotoxic T-lymphocytes. [15]. It has been established that nonspecific immune responses provided by monocytes and neutrophils are reduced. However, on the 14th day there is an increase in their number, which may be due to short-term stimulation of leukocytopoiesis. The activity of cells of a specific immune response - lymphocytes - remains elevated in all groups of animals, increasing to the maximum on the 7th and 30th days of the experiment. It has also been shown that cold exposure is accompanied by a decrease in the number of platelets, which we consider as their appropriate response to the effect of cold. Animal hypothermia activates the processes of erythropoiesis and, accordingly, leads to increased hematocrit values. These changes in the cellular composition of blood cells are manifested in the characteristics of the reaction of erythrocytes, platelets and leukocytes during cold exposure to animals, are natural and are confirmed in this study [4]. The thymus is the central organ of immunogenesis, on the functioning of which the protective reactions of the body depend. Various stress factors can have an effect on the immune organs. One of these factors is exposure to low temperatures. It was found that as a result of cold stress on the 7th, 21st and 30th days, there is a redistribution of the volume and cellular composition, various structural and functional zones, indicating a decrease in the functional activity of the thymus, an increase in the death of lymphocytes by apoptosis, a decrease in mitotic activity and the accumulation of macrophages. Morphofunctional data of the 14th day of the experiment indicate the development of compensatory and adaptive changes in the thymus to cold exposure, manifested as activation of cell division in the cortical substance and the cortico-medullary zone [1].

While moderate exercise is good for the human body and its immune system, exhausting excess exercise in cold conditions can be detrimental. When studying the effect of high physical activity when exposed to low temperatures (100-kilometer ultramarathon at temperatures from -1 °C to +1 °C) on individual immunological, biochemical and hematological parameters. Under these conditions,

there is an increase in the number of immature and mature neutrophils, as well as monocytes, while the number of lymphocytes and eosinophils did not change. The level of IgG increased, but the content of IgA and IgM remained unchanged. The number of platelets increased, while erythrocytes, hematocrit and hemoglobin did not change. The levels of lactate dehydrogenase (LDH) and creatine kinase (CK) increased, but alanine aminotransferase (ALT) did not change. The greatest change was noted in the increase in the number of immature neutrophils (1019.2%) and CPK levels (1077.6%). Thus, it has been shown that running a 100-kilometer ultramarathon in cold conditions leads to changes in several immunological, biochemical and hematological parameters, which indicates a serious burden on the body associated with increased susceptibility to the development of infections [28]. We studied indicators characterizing the state of cellular components of adaptive and innate immunity in practically healthy test volunteers aged 27 to 34 years. In peripheral blood, the content of the absolute and relative number of lymphocytes with the phenotype CD3+, CD3+CD4+, CD3+CD8+, CD19+, CD3-CD16+CD56+, CD3+CD16+CD56+, CD3+CD25+, CD45RA+, CD4+CD45RA+, as well as monocytes and granulocytes expressing signal pattern-recognizing receptors of the Toll-like (TLR) family TLR2, TLR4, TLR6 on their membrane. It has been shown that a single exposure at -70 °C has a significant effect on the cellular factors of the human immune system. Under the influence of ultralow temperatures, multidirectional changes are observed in the adaptive and innate components of human immunity, which are a reflection of a complex adaptive process caused by a stress response to a short stay in an air cryosauna at ultralow temperature [7].

A variety of factors, including metals, can affect the intensity of the reaction of programmed cell death. On the example of the child population living under the combined influence of chemical technogenic and extreme climatic factors of the Far North, an imbalance in the immune status was established, which is expressed in the excessive expression of membrane (HLA-DR+, CD95+, TNFR) and intracellular (p53, bax) indicators with the formation of a program cell death along the path of necrosis (in contrast to the comparison group, which was exposed to only natural extreme factors), which characterizes the state of immunodeficiency and a high risk of viral infections and their complications [2]. Apoptosis under conditions of exposure to strontium has been studied. We examined the children's population consuming drinking water with a high content of strontium (Sr2+) (n = 49). Exposure to strontium in vitro was characterized by a significant decrease in the level of expression of regulatory factors of apoptosis of the membrane marker CD95 and intracellular transcription protein p53 by 1.56 times and 1.68 times, respectively. At the same time, there was a significant decrease of 4.68 times in the number of AnnV-FITC+-PI cells, as well as a statistically significant increase of 1.35 times in the percentage of AnnV-FITC+PI+ cells. In addition, in all samples, the number of AnnV-FITC+PI lymphocytes was below the physiological norm and control values, and the number of samples where the content of AnnV-FITC+PI+ lymphocytes exceeded the established standards and control values was 30.8%. Thus, it has been experimentally proven that strontium at a concentration corresponding to the MPC for water bodies inhibits cell death via apoptosis with a high degree of reliability, switching to cell death by necrosis according to the criterion of phosphatidylserine content, detected in the test with annexin V. The obtained data revealed the ability of strontium to have a significant impact on the regulation and maintenance of cellular homeostasis, influencing the intensity of the apoptosis process by shifting the balance towards the implementation of cell death through necrosis and reducing the expression of regulatory factors. The results of the study can be used to identify and substantiate marker indicators of immune response disorders in assessing the environmental impact of strontium on public health in a specific factor environment [6].

**2. Infectious diseases and apoptosis.** The effect of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on the number of peripheral blood lymphocytes in most patients was studied. The results showed that the percentage of lymphocytes, CD4, and CD8+ T cells were reduced in patients with COVID-19 compared to the control group. In terms of clinical severity, lymphocyte counts, CD4+, CD8+ T cells, and NK cells were also reduced in severe cases compared to mild cases. The data also indicated an increase in mononuclear cell apoptosis in patients with COVID-19, which was more pronounced in severe clinical cases. The frequency of immune cells is a useful indicator for predicting the severity and prognosis of patients with COVID-19. These results could help explain the immunopathogenesis of SARS-CoV-2 and provide new biomarkers, therapeutic strategies, and vaccine candidates [21]. Although apoptosis is considered to be an innate cellular response to invading infectious pathogens, influenza A viruses have evolved to encode viral proteins that modulate host cellular apoptosis in such a way as to support efficient virus replication and propagation [19]. Recent trends in sepsis research indicate that the greatest mortality occurs during a prolonged immunosuppressive state, when patients die from secondary infections within weeks or months due to post-sepsis "immune paralysis". Alteration of immune cells caused by uncontrolled apoptosis is considered the main cause of significant immunosuppression. In particular, lymphocyte apoptosis increases the risk of secondary infections and adverse outcomes [3]. In most parvovirus infections, cell death enhances the spread of the virus and causes tissue damage, often resulting in disease. Cell cycle arrest also causes cytopathic effects in infected cells and is sometimes a prerequisite for apoptotic cell death. The mechanisms of cell death caused by parvovirus infections differ depending on the strain infecting the parvovirus and the cell lines involved. Apoptosis, however, is a common form of cell death caused by parvoviruses [17].

Well-studied intracellular bacterial pathogens such as Salmonella, Yersinia, and Listeria increase their chances of survival by disrupting programmed host cell death (PCD), an internal cellular response that kills cells under certain stressors. Although Staphylococcus aureus is considered a destructive extracellular organism, there is growing evidence that S. aureus is an experienced intracellular pathogen. WITH . aureus is able to enter, multiply, and persist in host cells to avoid bactericidal immune disorders (eg, opsonization and circulating antibodies), antibiotic treatment, and detection by surface receptors. Although staphylococcal toxins cause a wide range of biological consequences leading to apoptosis, they can either inhibit apoptosis to ensure the survival of infected host cells [28]. The molecular mechanism of bacterial effectors includes secreted proteins that bind to the signaling pathways of apoptotic cells and inhibit them [21, 27].

**3. Effect of various substances on apoptosis.** Various drugs also affect the intensity of apoptosis and the ability to proliferate. One study evaluated the effects of psychotropic drugs (lithium and valproic acid) in patients with bipolar disorder. According to the results of the study, T-lymphocytes of patients with bipolar disorder, especially those who re-

ceived lithium, have a reduced ability to proliferate compared to healthy people. In vitro studies have shown that valproic acid reduces the number of cell divisions and the percentage of proliferating cells regardless of health status, but mainly at very high doses, while lithium does not significantly affect the ability to proliferate T-lymphocytes of patients. The lymphocytes of patients with BD are also more prone to apoptosis compared to healthy people, which is associated with a high expression of the proapoptotic protein. Lithium in vitro protected the lymphocytes of patients from apoptosis in proportion to the dose used. Mood stabilizers used to prevent relapses of the disease have an anti-apoptotic effect on T-lymphocytes of patients with BD, but they are not able to improve their ability to proliferate [32].

The immunomodulatory effect of Nigella sativa (NS) fatty oil has been revealed. Studies have shown that unrefined, cold-pressed black cumin seed oil inhibits lymphocyte proliferation and induces lymphocyte apoptosis in a dose-dependent manner. In this study, we examined the immunomodulatory properties of essential oil obtained from NS seeds by hydrodistillation and its two main components: thymoquinone (TQ) and p-cymene. In summary, NS essential oil significantly inhibits CD4+ and CD8+ T-lymphocyte proliferation, induces cell death in a dose-dependent manner, and reduces the expression of CD28 and CD25 antigens required for lymphocyte activation. TQ inhibited T-lymphocyte proliferation and induced cell death, especially at high concentrations. Meanwhile, p-cymene did not affect the proliferation of lymphocytes. However, its high concentration induced cell necrosis. Thus, Nigella sativa essential oil has potent immunomodulatory properties that are at least partially related to the TQ component [23].

One of the substances that have an impact on the cellular immune response are β-glucans. They are polysaccharides usually obtained from the cell wall of bacteria, fungi, yeast and the aleurone layer of cereals. β-glucans are polymers based on β-1,3 glucose in a linear structure, but differ in the length of their main branches, bonds and branching patterns, resulting in high and low molecular weight β-glucans. They are well known cellular response modifiers with immunomodulatory, nutraceutical and health benefits, including antitumor and proapoptotic properties. β-glucan extracts have shown positive effects in controlling tumor cell proliferation and activating the immune system. The immunomodulatory effect of β-glucans enhances the body's antitumor defense against cancer. In line with the above, many studies have shown that treatment with β-glucan leads to the induction of apoptotic death of cancer cells. The ability of β-glucans to stimulate apoptotic pathways or proteins involved in apoptosis opens up a new area in cancer therapy. β-glucan may be a potential therapeutic agent for cancer treatment [24]. It has been proven that propolis and its components exhibit proapoptotic activity, inducing both mechanisms of cell death [26].

Extracellular calcium plays an important role in the processes of programmed cell death. It was found that the incubation of lymphocytes in Hank's solution, which does not contain calcium ions, and in Hank's solution with excess calcium (13 mmol/l) induces significant changes in metabolic processes and the state of the surface of lymphocytes compared with those for cells in the presence of calcium at a normal concentration (1 .3 mmol/l). These disorders initiate the process of lymphocyte death under conditions of calcium deficiency and excess, predominantly by the mechanism of apoptosis (mitochondrial pathway) and, to a lesser extent, necrosis [11].

Autophagy and apoptosis are two fundamental pathophysiological mechanisms of cell fate regulation. However, the signaling pathways of these processes are largely interrelated. The interaction of autophagy and apoptosis involves signal transduction pathways that are highly dependent on Ca 2+ . Indeed, the functions of Ca 2+ as a second messenger are critical to the coordination of fundamental physiological functions, including cell survival and growth, neuronal development, and/or maintenance of cellular functions. Coordination between Ca 2+ proteins/pumps/channels and Ca 2+ storage in various organelles is critical to maintaining cytosolic Ca 2+ levels that maintain the spatial resolution required for cellular homeostasis. Ca 2+ homeostasis is regulated by store-operated Ca 2+ entry (SOCE), which is activated by depletion of Ca 2+ from internal ER stores. Ca 2+ has been shown to control opposite functions, such as autophagy, which promote cell survival; on the other hand, Ca 2+ also regulates programmed cell death processes, including apoptosis. It has recently become apparent that a complex network of lipid-lipid and lipid-protein interactions contributes to the activation of various signaling pathways that regulate cellular homeostasis. Thus, specific plasma membrane microdomains called lipid rafts regulate various signaling pathways involved in specific cellular programs, including proliferation, apoptosis, differentiation, stress response, and autophagy, thus determining cell fate. However, lipid rafts are present not only in the plasma membrane, but also in the membranes of intracellular organelles, including the ER, the Golgi apparatus, endosomes, and lysosomes. These sites can catalyze key reactions that have a significant impact on the regulation of intracellular transport and sorting, cholesterol homeostasis, and cell fate. Mitochondrial associated membranes (MAMs) have been classified as critical "hubs" in the regulation of apoptosis, autophagy, and tumor growth. The recent discovery of lipid rafts as physical and functional platforms in MAMs has contributed to the elucidation of the mechanisms underlying the early stages of the autophagic process. In particular, it appears that microdomain proteins like ER lipid rafts, i.e. proteins 1 (ERLIN1) and 2 (ERLIN2) associated with the ER lipid raft, can regulate cell survival and death. The putative role of ERLIN in the degradation of the calcium channel (inositol-1,4,5-triphosphate receptor) may explain their role in the mechanism of autophagy, having a significant impact on the pathogenesis of several human diseases.

**4. Apoptosis and aging.** Researchers cannot yet predict how long a person can live. Life expectancy has risen steadily over the past century, but the quality of life may not always have gone hand in hand with it. Future generations will face the challenges of increasing life expectancy along with the emergence of new age-related diseases. A better understanding of the aging process is critical to improving, if not preventing, these predicted new diseases of old age. One of the mechanisms responsible for healthy aging is the efficient maintenance of physiological, biochemical and immunological functions. To do this, the body needs to create new cells to replace old ones and cause the old and damaged cells to disappear. Apoptosis is involved in all these processes. However, if apoptosis is not regulated, diseases associated with premature aging are likely to occur. All molecular mechanisms of aging can regulate programmed cell death through apoptosis. In mitotic and post-mitotic cells, low levels of apoptosis promote accumulation of damaged cells, aging, and genomic instability, but in response to injury/damage, low levels of apoptosis prevent tissue destruction and promote cell survival, proliferation, damage repair, and regeneration. In mitotic and post-mitotic cells, physiological levels of apoptosis have several advantages

for the aging process. In fact, eliminating dysfunctional cells and reducing the accumulation of senescent cells improves homeostasis and lifespan. A moderate increase in apoptosis in mitotic highly proliferative cells improves the rate of cell renewal, while in postmitotic cells, apoptosis promotes cell loss and tissue dysfunction [18,20].

The cellular theory of aging states that human aging is the result of cellular aging, in which an increasing proportion of cells reach senescence. Aging is an irreversible growth arrest that occurs in response to damaging stimuli such as DNA damage, telomere shortening, telomere dysfunction, and oncogenic stress, resulting in the suppression of potentially dysfunctional, transformed, or senescent cells. Cellular senescence is characterized by irreversible arrest of the cell cycle, flattened and enlarged morphology, resistance to apoptosis, changes in gene expression and chromatin structure, expression of aging-associated β-galactosidase (SA-β-gal), and the acquisition of an aging-associated secretory phenotype [16, 18 ].

**Conclusion.** So, the programmed cell death, or apoptosis, is the most important process of maintaining the homeostatic constancy of the body. Therefore, apoptosis is believed to be critical in terms of embryonic development throughout the growth of the organism, promoting tissue renewal and disposal. from inflammatory cells. Apoptosis begins with the triggering of various intra- and intercellular signals and stimulations that involve a number of extrinsic or intrinsic pathways of apoptosis. Understanding these complex pathways offers new approaches to the clinical management of deadly human diseases.

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# THE ROLE OF THE BDNF (RS6265) AND CNTF (RS1800169) GENE POLYMORPHIC VARIANTS IN THE DEVELOPMENT AND PROGRESSION OF NEUROLOGICAL DISORDERS

DOI 10.25789/YMJ.2023.83.25

УДК 616.8:575.174.015.3

In recent decades the contribution of polymorphic variants of genes encoding neuroinflammation and neuroprotection proteins in pathology of the nervous system has been actively studied. Numerous studies have demonstrated the most important structural and functional role of single nucleotide variants in the BDNF and CNTF genes in the brain. This review provides evidence of the association of polymorphic loci of the BDNF and CNTF genes with a number of neurological disorders. It was found that an increased risk of developing depressive disorders, Alzheimer's and Parkinson's diseases are characteristic of the BDNF rs6265 polymorphism carriers. Moreover, the above mutation affects the length of stay in rehabilitation and the duration of remission in patients with substance dependence. A number of authors provide contradictory information about the relationship of the BDNF rs6265 genetic variant with changes in neurotrophin levels in schizophrenia. The BDNF rs6265 A/A genotype carriers in Caucasian and Asian populations showed an increased risk of the disease. The CNTF rs1800169 genetic variant does not affect the risk of schizophrenia in general but may play a more prominent role in its clinical manifestations together with other CNTF gene mutations. Some studies have shown an association of the rs1800169 polymorphism in the CNTF gene with schizophrenia spectrum disorders. A number of studies have confirmed a negative association between the rs1800169 polymorphism in the CNTF gene and Alzheimer's disease. Further studies are needed to clarify the role of the BDNF and CNTF genetic variants in pathology of the nervous system and to find an effective treatment.

**Keywords:** brain-derived neurotrophic factor, ciliary neurotrophic factor, the BDNF gene, the CNTF gene, SNP markers, genetic predisposition, neurological disorders.

**Introduction.** Nowadays neurological disorders remain one of the leading causes of disability and premature death and contribute significantly to the global burden of disease [5]. The development of molecular genetic methods has led to an increasing number of association studies of polymorphic variants of genes encoding proteins of neuroinflammation and neuroprotection which include brain-derived neurotrophic factor and ciliary neurotrophic factor.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and expressed in the central and peripheral nervous system, vascular endothelium, leukocytes, platelets, megakaryocytes, and muscles. Its functions are carried out through signaling pathways activated by TrkB (tropomyosin receptor kinase B) and p75NTR (p75 neurotrophin receptor) receptors. BDNF is found to be essential for the proper functioning of the nervous system and implicated in the pathogenesis of neural diseases. This neurotrophin modulates the work of dopaminergic neurons, myelination of nerve fibers, stimulates axon growth, synaptogenesis, and participates in the regulation of neuroplastic processes (long-term potentialization and depression of synaptic transmission). In the developing nervous system it promotes synaptic pruning, and also performs a neuroprotective function when being exposed to damaging factors. In addition, BDNF participates in the processes of oncogenesis, angiogenesis, gluconeogenesis and others [3, 25].

Ciliary neurotrophic factor (CNTF) belongs to the cytokines of the interleukin-6 family and performs a number of functions by binding to the high-affinity receptor complex CNTFRα/GP130/LIFRβ (CNTF receptor α/glycoprotein 130 receptor β/leukemia inhibitor factor receptor β). This cytokine supports self-renewal and differentiation of neural stem cells, stimulates neurite growth in sensory neurons, inhibits apoptosis of spinal ganglion neurons, accelerates regeneration of motor neurons and skeletal muscles, and participates in mechanisms of cardioprotection. CNTF plays an important role in the pathogenesis and treatment of psychiatric disorders, affective behavior, neurodegenerative diseases, spinal cord injury, and retinal degeneration. In addition, it is essential for energy metabolism: it activates in the hypothalamus pathogenetic pathways related to leptin metabolism. CNTF expression has been confirmed in astrocytes, Schwann cells, retinal pigment epithelium, and Müller cells [12].

**The aim** of this review is to update, systematize and summarize the data of scientific publications on the role of single nucleotide variants of the BDNF and CNTF genes in the pathogenesis of neurological disorders. To achieve this goal we have searched for English and Russian articles (up to 2023 inclusive) in Pubmed, Google Scholar, and eLibrary databases and have used the descriptive method.

**The rs6265 polymorphism of the BDNF gene.** The human BDNF gene is located on the short arm of chromosome 11 (locus 11p14.1) and includes

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