Review Article

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Cell Death. Morphofunctional Features

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ABSTRACT

There are morphological and biochemical classification of types of cell death. Morphological classification of types of cell death [1]. Relevant for an adequate characterization of cell damage is the assessment of types of cell death. Most of the biochemical varieties of accidental and regulated cell death fit into four morphological types: apoptosis, autophagic death, senescence, necrosis, and mitotic catastrophe. The information presented in the work on the functional features of cell death will serve as a fundamental basis for further study of destructive processes in cytology with the subsequent implementation of the results obtained into clinical practice.

Keywords: Apoptosis; Cell Death; Markers; Mechanisms

Abbreviations: PARP-C: Poly-Adp-Ribose Polymerase; DR: Death Receptors; APAF: Apoptotic Protease Activating Factor; FADD: Fas-Associated Protein with Death Domain; TRADD: TNF-R-Adapter-Protein with Death Domain; NCCD: Nomenclature Committee on Cell Death; NMDA: N-Methyl-D-Aspartate

Review

There are morphological and biochemical classification of types of cell death. Morphological classification of types of cell death [1]. Relevant for an adequate characterization of cell damage is the assessment of types of cell death. Most of the biochemical varieties of accidental and regulated cell death fit into four morphological types: apoptosis, autophagic death, senescence, necrosis, and mitotic catastrophe [2,1]. Senescence is a form of cell cycle arrest in embryogenesis, tumor growth, and aging. During the period of antenatal ontogenesis, the cells of the apical ectodermal ridge and the neural plate, which are in a state of senescence, provide the processes of growth and differentiation of the nervous tissue. There are suggestions that senescence is a programmed mechanism that ensures the development of the organism [3-7]. Autophagy. This type of cell death is manifested by the degradation of organelles and cytoplasmic material with the participation of specific intracellular membrane structures - autophagosomes, which are double-membrane formations surrounding cell organelles or part of the cytosol to be destroyed. Autophagosomes fuse with lysosomes to form autophagolysosomes. In some pathological conditions, excessive activation of autophagy can cause a form of cell death - autophagic cell death [8,9].

Morphologically, autophagic death is manifested by partial condensation of chromatin, nuclear pycnosis, the appearance of autophagosomes and autophagolysosomes, deformation of the Golgi apparatus, expansion of cisterns of the endoplasmic reticulum, and an increase in the permeability of mitochondrial membranes. With this type of cell death, no fragmentation of the nucleus and cell is observed, there is no degradation of DNA to the nucleosomal level, long-term preservation of microtubules and intermediate filaments is characteristic, unlike apoptosis, there is no activation of caspases. Autophagy ensures the destruction of «long-lived proteins» and damaged organelles [8,9]. The activating factors of autophagic cell death are: lack of nutrients, the presence of damaged organelles, proteins with a changed structure due to oxidative or toxic stress, as a reaction to starvation, during the implementation of immune defense reactions [8-10]. Mitotic catastrophe is a special form of cell death with signs of pathology of mitosis - lag of chromosomes in meta- and anaphase, the presence of multipolar and multigroup meta- and anaphases. This type of cell death occurs both during mitosis and in interphase [11].

The most common cause of mitotic catastrophe is a malfunction of the G2-checkpoint, a checkpoint during the transition from the G2 phase to mitosis. This determines the fate of the cell depending

on the efficiency of DNA replication. Disturbances in the interaction of checkpoint proteins lead to cell death during mitosis due to the impossibility of repairing DNA damage. Another mechanism leading to mitotic catastrophe is microtubule damage and spindle alteration. This process can be modeled using colchicine, vinblastine, or vincristine [11]. Abnormalities in mitosis can be the cause of the formation of viable polyploid cells or death with the participation of caspases. In such cells, micro- and multi-nucleus are observed, there are no phenomena of chromatin margination and condensation, which distinguishes this type of cell death from apoptosis. During a mitotic catastrophe, internucleosomal DNA breaks, which are detected by the TUNEL-method, are usually absent. The formation of one or more micronuclei is a morphological marker of mitotic catastrophe. However, during apoptosis and necrosis, similar structures can also be detected [11]. Mitotic catastrophe can be detected using light and electron microscopy, as well as immunohistochemical methods, which allow studying the distribution of markers p53, Ki-67, penetrin, gamma-tubulin [11].

A mitotic catastrophe is initiated by a malfunction of the mitotic apparatus during the M-phase of the cell cycle [11]. Apoptosis is a regulated cell death involving a genetically programmed molecular mechanism that can be modulated by pharmacological or genetic influences. The phenomenon of apoptosis plays an important role in the destruction of cells during embryogenesis and organogenesis, as well as during the involution of organs and tissues in an aging organism, during the immune response and other processes [12-15]. Apoptosis is an energy-dependent process and, as a rule, is not accompanied by the development of an inflammatory reaction [15].

Morphological Features of Apoptosis

Apoptosis is manifested by chromatin condensation, DNA fragmentation and nuclear disintegration (karyorrhexis), rounding of cells, retraction of processes, loss of microvilli, loss of folding of the cytoplasmic membrane, protrusion of sections of the outer cytoplasmic membrane (blebbing), which often ends in the formation of membrane microparticles [12-17,10]. Until the late stages of the process, the integrity of the membrane is preserved, the size of the cell decreases and its subsequent fragmentation into membrane vesicles with intracellular contents - apoptotic bodies, which are subsequently phagocytosed by macrophages and neighboring cells [12-14,10,18,19]. A cell during apoptosis decreases in size, its cytoplasm becomes denser. Organelles are arranged more compactly. It is assumed that changes in the shape and volume of the cell are a consequence of the activation of the transglutaminase enzyme, which causes the formation of cross-links between cytoplasmic proteins, which leads to the formation of a kind of shell under the cell membrane [15,20,18].

The most characteristic manifestation of apoptosis is the condensation of chromatin along the periphery of the nucleus with the formation of clearly defined seals of various shapes and sizes. In this case, the core can be torn into two or more fragments [14,15,20,21,17]. Chromatin condensation is caused by the cleavage of nuclear DNA by the action of calcium-dependent endonuclease at the sites that bind individual nucleosomes, which leads to the formation of a large number of fragments [14,15,19-21,17]. In the cytoplasm, cavities and apoptotic bodies are formed, consisting of densely packed organelles, with or without nuclear fragments [15,17]. Immunohistochemical markers of apoptosis are apoptosis inducing proteins (Bad, Bax), apoptosis inhibitory proteins (Bcl-2, Bcl-XL). Also often determined are antibodies to the p53 protein, cytokeratin-18 cleavage products (C-CK18), activated caspases-3, -1 and -7, phosphorylated histone H2AX (gammaH_2AX), poly-ADP-ribose polymerase (PARP-C), apoptosis inducing factor (AIF). Annexin V binding sites are also determined [14,15,20,21].

Physiological Role of Apoptosis

- Controls the number of cells in organs and tissues.
- Participates in the regulation of the body's immune mechanisms.
- Elimination of virus-infected cells.
- Tumor cells (interaction of Fas-R and Fas-L).
- Activity of the inflammatory process and immune response by stimulating the death of activated T-lymphocytes.
- Prevents the development of autoimmune damage to trans-barrier organs (testis, eyes) that have Fas-L receptors that interact with Fas-R autoreactive T-lymphocytes, penetrating into them, die due to apoptosis due to their interaction with lymphocytes.
- Elimination of autoreactive T- and B-lymphocytes [15,19].

Reasons for Apoptosis

- Programmed cell death during embryogenesis.
- Hormone-dependent involution of organs.
- Elimination of individual cells in tumors during its regression or active growth.
- Death of lymphocytes after depletion of cytokines.
- Pathological atrophy of hormone-dependent organs (atrophy of the prostate gland after castration).
- Pathological atrophy of parenchymal organs after obstruction of the excretory ducts.
- Action of cytotoxic T-lymphocytes (graft rejection).
- The effect of damaging factors in small doses (viruses, temperature, ionizing radiation, antitumor drugs) [12-15,10,19,17].

The Following Stages of Apoptosis are Distinguished

- Stage of induction (features depend on the nature of the stimulus acting on the cell).

- Effector stage (intracellular mechanisms of cell death are switched on).
- Stage of degradation (destruction of vital cellular components with the appearance of morphological signs of apoptosis) [15].

The implementation of apoptosis occurs with the participation of enzymes - caspases.

There are Two Groups of Caspases:

- Initiating caspases (2, -8, -9, -10), which are activated in response to the action of stimuli that trigger apoptosis.
- Effector caspases (3, -6, -7) are activated by initiating caspases [22].

Caspases are cysteine proteases that cleave substrates at the location of aspartic residues in the molecule [22].

The Targets for Effector Caspases are:

- Proteins involved in transcription and DNA repair, such as poly-(ADP-ribose) polymerase.
- Ore proteins (laminin A).
- Cytoskeletal proteins (fodrin and gelsolin).
- DNase inhibitor [22].

Caspase function is controlled by a family of proteins called «protein inhibitors of apoptosis». Members of this family of proteins bind to caspases 3, -7 and -9 and inhibit their activation [22].

Ways to Trigger Apoptosis:

- Through the activation of «death receptors» (DR).
- Mitochondrial (release of cytochrome c into the cytoplasm, activation of APAF-1 (apoptotic protease activating factor) and formation of the apoptosome, mediated action of the p53 protein).
- Through the cell membrane: mediated by the «perforin-granzyme» system.
- By expression of apoptosis promoter genes Bad, Bax, Rb, p53 or inhibition of anti-apoptotic genes - Bcl, Bcl-XL, etc [13-15,20,21].

The way to trigger apoptosis through the activation of membrane «death receptors.» Cell membranes have special «death receptors» (DR - Death Receptors). These include the Fas receptor (Fas-R), the receptor for tumor necrosis factor-α (TNF-R) and the death receptors DR3, DR4 and DR5 [4,7,14,15,25]. The interaction of Fas-Ligand (Fas-L) with Fas-R, TNF-α with TNF-R or TRAIL (TNF-related apoptosis inducing ligand, TNF-α-related apoptosis inducing ligand), with DR4 or DR5 causes aggregation of these receptors. Fas-L is a cell membrane protein of the TNF family, present on cytotoxic T-lymphocytes and NK-cells, as well as on cells of «immune-privileged organs» and on cells of malignant tumors. It can temporarily appear on other cells under the influence of pro-inflammatory cytokines [15,20]. After the interaction of the death receptor with the corresponding ligand, aggregation of death receptors occurs, after which special adapter proteins are sent to the cytoplasmic regions (domains) of aggregated death receptors: FADD (Fas-associated protein with death domain), TRADD ligands (TNF-R-adapter-protein with death domain) that interact with TNF-R. The resulting complex activates the initiating caspases (pro-caspase-8 or -10), which activate first the effector caspase-3, and then caspases-6 and -7.

Mitochondrial Pathway for Triggering Apoptosis

There is a mitochondrial mechanism for enhancing the function of effector caspases. At the same time, caspase-3 in the active state cleaves the Bid cytoplasmic protein, which then moves to the mitochondria and integrates into the membrane, which leads to the release of cytochrome c from the mitochondria into the cytosol. Cytochrome c interacts with APAF-1 and pro-caspase-9 to activate the latter and activate pro-caspase-3, which in turn activates caspases-6 and 7 [13].

The reasons that trigger apoptosis through a change in mitochondrial function are:

- Deficiency of growth factors in the environment surrounding the cell.
- Increase in the formation of reactive oxygen species in the cell.
- DNA damage.
- The effect of glucocorticoids on lymphocytes, thymocytes, etc [13].

Under the influence of these stimuli, the function of proteins belonging to the Bcl-2 family changes. The proteins of this family are divided into two classes [15,20]. Proteins of the first class inhibit apoptosis. They are embedded in the outer membrane of mitochondria and regulate membrane permeability, as well as reduce the formation of ROS. Representatives of this class of proteins are Bcl-2 and Bcl-xL [12,15,20,21]. Proteins of the second class of the Bcl-2 family stimulate the development of apoptosis. These proteins are located in the cytosol, but then move to the mitochondrial membrane, where they interact with the representatives of the first class - Bcl-2 and Bcl-xL proteins, inhibiting them. Members of the class II proteins of the Bcl-2 family are Bid, Bad, Bax, and others [12,14,15,20,21]. The activation of representatives of the second class Bcl-2 causes an increase in the permeability of the inner mitochondrial membrane, which leads to swelling of the mitochondrial matrix and rupture of the outer membrane. When the function of members of the Bcl-2 family that inhibit apoptosis is suppressed, a “non-selective megachannel” can form in the mitochondrial membrane, which increases membrane permeability, which leads to the release of cytochrome c and the DIABLO protein from mitochondria into the cytosol [12,14,15,20,21 ,9,19,22,25,7,17].

Cytochrome c that enters the cytosol interacts with APAF-1, attracting caspase-9, which leads to the formation of a protein complex, the apoptosome. In the presence of ATP, caspase-9 is activated. The DIABLO protein inactivates protein inhibitors of apoptosis, which leads to the activation of caspase-3 [12,16,15,20,21,17].

The Pathway of Apoptosis Triggering by the «Perforin-Granzyme» System

This apoptosis triggering pathway plays a role in the mechanism of target cell death under the influence of cytotoxic T-lymphocytes and NK cells, participating in the body's defense against viruses, tumor cells, as well as in the mechanisms of autoimmune tissue damage and transplant rejection [13,15]. After recognition of the target cell, cytotoxic T-lymphocytes and NK cells, using perforin, cause the formation of a pore in its plasma membrane, through which granzyme B enters, activating caspase-3 [13,15,22].

Apoptosis Initiation Pathway Associated with the Action of P53 Protein and Other Apoptosis Promoters

The p53 protein, which plays an important role in the mechanisms of cell protection against damage, is constantly formed in various cells. In normal cells, the content of the p53 protein is negligible due to its rapid degradation after formation. DNA damage causes stabilization of the p53 protein, which increases its concentration in the cytosol. The p53 protein is a transcription factor. It can bind to the promoters of a number of important genes: to the p21 protein gene, activating it, which leads to the formation of its product, which inhibits cyclin-dependent kinases that "stop" the cell at the G1 or G2 stage of the cell cycle [10,12-19]. When DNA repair fails, p53, through the activation of the corresponding gene, increases the formation of the Bax protein, which triggers apoptosis by changing the function of mitochondria. The p53 protein also stimulates the formation of reactive oxygen species, which change the state of the mitochondrial membrane and cause the release of cytochrome c into the cytosol. In addition, when DNA repair is impaired, the p53 protein increases the formation of Fas-R, facilitating its transport from the Golgi complex to the cell membrane, which activates apoptosis under the influence of the Fas ligand [10,12-19].

Recognition of Apoptotic Cells and Apoptotic Bodies by Phagocytes

Intracellular phenomena during apoptosis lead to asymmetry of cell membrane phospholipids. As a result, phosphatidylserine appears in the outer lipid layer of apoptotic bodies, which under normal conditions is located in the inner lipid layer of the membrane. Phosphatidylserine is recognized by scavenger receptors on phagocytes. These receptors can also recognize altered LDL and other polyanionic ligands [12-15,17,18,20,21]. Recognition of apoptotic cells by phagocytes can also occur through CD36 receptors. First, phagocytes secrete thrombospondin, which binds to CD36. Thrombospondin then binds to the appropriate sites on the surface of apoptotic cells. In addition, receptors for the C1q component of the complement system and a receptor for vitronectin are involved in the recognition of apoptotic cells [12-15,17,18,20,21]. After recognition of apoptotic cells and apoptotic bodies, they are taken up by phagocytes. At the same time, phagocytosis of apoptotic bodies is not accompanied by the formation of substances that stimulate the development of inflammation. On the contrary, phagocytes form substances with anti-inflammatory action: transforming growth factor 1, prostaglandin E2 and interleukin-10 [14,20,21].

Approaches to the Classification of Damage and Death of Nerve Cells

With the development of the process of neurodegeneration, the death of predominantly nerve cells and the activation of the glial component of the nervous tissue occur. The vast majority of neurons during the development of the neurodegenerative process die not from the direct impact of the lethal factor, although its action at the initial stages is not excluded, but as a result of the gradual depletion of defense mechanisms and the activation of the self-destruction program [12,1,21,7]. The first studies of irreversible destructive changes occurring in cells began to be carried out shortly after the development of the cellular theory by M. Schleiden, T. Schwann (1838). In the study of cell death in the nervous system, R. Virchow (1858) identified two types of degenerative processes: passive «necrosis» and the active process of cell destruction in «living tissues» - «necrobiosis» (Clarke P. G., 2012). R. Virchow's classification to a certain extent corresponds to modern concepts of necrosis and apoptosis [11,1,15,21,7].

In 1990, P. G. Clarke proposed a classification of types of cell death that is currently relevant: I - apoptosis, II - autophagy, III - non-lysosomal cell death - corresponds to necrosis. In 2005, the Nomenclature Committee on Cell Death (NCCD) recommended a classification that further characterized other variants of cell death. According to modern concepts, a cell can be considered dead if one of three morphological and molecular criteria is identified: loss of the integrity of the cytoplasmic membrane, complete fragmentation of the cell (including its nucleus) with the formation of individual apoptotic bodies, and absorption of the dead cell (or its fragments) by another cell [15]. The modern classification of cell death (apoptosis, necrosis, autophagy, senescence, mitotic catastrophe) is based on morphological manifestations of cell death, molecular (biochemical) criteria (intracellular processes occurring with or without participation of various proteases and nucleases), functional aspects (regulated or accidental death, physiological or pathological) and immunological characteristics of the process (immunogenic and non-immunogenic cell death) [12,1,21,7].

All types of cell death fit into two main non-overlapping groups: regulated cell death and accidental (random) cell death. Accidental cell death occurs as a result of physical (elevated temperature, high pressure), chemical (uncompensated changes in pH level) and mechanical damaging factors. This type of cell death develops rapidly and is resistant to the effects of pharmacological agents. The concept of «accidental cell death» is close to the more widely used concept of «necrosis»[16,15,17]. To accurately determine the type of cell death,

it is necessary to use morphological methods, primarily electron microscopy. A combination of at least two research methods is recommended: a method for visualizing morphological changes and determining biochemical changes inside the cell [12,1,21,7].

Biochemical Classification and Features of Neuronal Apoptosis Types

According to the biochemical classification, there are several different mechanisms of neuronal apoptosis that have similar morphological manifestations: perikaryon swelling, neuropil destruction, chromatin condensation, DNA fragmentation followed by karyorrhexis [15,19]. The external (receptor) mechanism of apoptosis is induced by extracellular stress signals that are perceived by specific transmembrane receptors [19]. The initiating factors of the mechanism involving the internal pathway of apoptosis are intracellular changes, such as DNA damage, oxidative stress, cytosolic calcium overload, excitotoxicity (hyperstimulation of glutamate receptors in the nervous system), accumulation of denatured proteins in the endoplasmic reticulum, and others. The main mechanism for the development of the internal pathway of apoptosis is an increase in the permeability of mitochondrial membranes. This type of cell death can be caspase dependent or independent of caspases [19]. By caspase-dependent cell death, as a rule, we understand the process carried out by caspases and suppressed by their broad-spectrum inhibitors, for example, N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone (Z-VAD-FMK) [19,22]. The caspase-independent pathway of cell death is characterized by chromatin lysis and is accompanied by depletion of NAD+ and ATP [19,22].

Excitotoxicity refers to neuronal-specific mechanisms of cell death, which occurs with excessive or prolonged activation of excitatory amino acid receptors (aspartate, glutamate). Overactivation of NMDA (N-methyl-D-aspartate) glutamate receptors leads to changes in the level of intracellular calcium, depolarization of the mitochondrial membrane, an increase in free radicals, and activation of caspases. Also, activation of glutamate receptors leads to an increase in the level of cAMP and the release of Ca2+ from intracellular depots. The toxic effect of glutamate contributes to the deposition of β-amyloid in the brain, and the activation of NMDA receptors leads to pathological phosphorylation of the τ-protein, the main component of neurofibrils. The death of neurons as a result of excitotoxicity is a mixed form of cell death, combining signs of necrosis and apoptosis. The early stages of cell death are characterized by swelling, vacuolization of the cytoplasm and destruction of the membrane, i.e., they are manifested by signs of necrosis. However, excitotoxicity results in internucleasome DNA degradation, chromatin fragmentation and condensation, and caspase activation, which is typical of apoptosis. Excitotoxicity, as a type of cellular degeneration, is involved in the pathogenesis of cerebral ischemia, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, and a number of other neurodegenerative diseases [2,1,21]. Ferroptosis is an iron-dependent form of regulated cell death, controlled by glutathione peroxidase-4 and glutathione-dependent enzyme. With ferroptosis, the density of mitochondrial membranes increases and a decrease in their size is observed [2,1,21].

Apoptosis Dysregulation

Dysregulation of apoptosis is manifested by its enhancement or suppression [15,20,19]. Suppression of apoptosis can lead to an increase in cell survival. This contributes to tumor growth and the development of autoimmune diseases [15]. Activation of apoptosis increases the likelihood of cell death. In this regard, apoptosis is involved in tissue and organ cell damage in: neurodegenerative diseases characterized by loss of neurons, ischemic damage to the myocardium and other organs, HIV-infection [2,1,15,20,21,19].

Pathology of Apoptosis

Mutation of the TNF-R1 gene leads to the development of «congenital periodic fever syndrome» due to a violation of the mechanism of suppression of the cell response to TNF. Altered TNF-R1 is expressed on leukocytes, but its removal from the membrane is impaired. At the same time, the content of the soluble form of TNF-R1 in the blood decreases, but it retains the ability to bind TNF, competing with cellular TNF-R1 for TNF. Symptoms of «familial periodic fever» are attacks of transient fever, inflammation of the serous and synovial membranes, myalgia, periorbital edema, pain in the scrotum, inguinal hernia [12,14-16,18-21,23]. Mutations of the Fas-R gene can lead to changes in the structure of the extra- and intracellular parts of the receptor. Fas-R mutations are most common in bladder tumors, Hodgkin's disease, and tumors of the stomach and intestines. Fas-R mutations provide resistance of tumor cells to NK cells and T-lymphocytes, which allows them to express their own Fas-L at a high level for protection against the body's immune system and invasion into surrounding tissues [12,14-16,19,20].

Mutation of the Fas-R gene also leads to the development of type I lymphoproliferative syndrome (ALPS I), accompanied by proliferation of lymphocytes and autoimmune organ damage. Patients are present with splenomegaly and hepatomegaly, enlarged lymph nodes, immunoglobulinemia, lymphocytosis, and lymphomas. At the same time, lymphocytes are resistant to death stimulated by the interaction of Fas-L with Fas-R [12,14-16,19-21,23]. Mutations in the Fas-L gene result in a lymphoproliferative syndrome similar to systemic lupus erythematosus [6,12,14-16,18-21,23]. Mutation of the perforin gene leads to familial hematophagocytic lymphohistiocytosis. The disease begins in childhood and is characterized by an increase in the content of activated lymphocytes and monocytes. There is an increased expression of pro-inflammatory cytokines: γ-interferon, interleukin-1, interleukin-6 and TNF. The cytotoxic effect of T- and NK-cells is impaired. The disease is manifested by fever, frequent viral infections, pancytopenia and hepato-splenomegaly [6,12,14-16,18-21,23].

Mutation of the caspase-10 gene leads to the development of type II autolymphoproliferative syndrome (ALPS II). The function of lymphocytes and dendritic cells is disturbed, they accumulate in the paracortical zones of the lymph nodes. Dendritic cells become resistant to apoptosis. The regulation of the immune response is disrupted.

The main manifestations of the syndrome: lymphadenopathy, hepatosplenomegaly, hyperimmunoglobulinemia with the presence of a large number of autoantibodies, with autoimmune hemolytic anemia and lymphocytosis [6,12,14-16,18-21,23]. Mutation of the Bcl-10 gene (B-cell lymphoma leukemia 10) leads to the development of Bcl-10 resistance to apoptosis signals, disruption of the mechanism of NF-kB activation and stimulation of cell proliferation [6,12,14-16,18-21,23]. Mutations in the p53 gene provide cell resistance to apoptosis [6,12,14-16,18-21,23]. Mutations of the Bax gene are observed in tumors of the intestine and blood system and also contribute to cell resistance to apoptosis [6,14-16,18-21,23]. Mutations in the Bcl-2 gene cause its excessive expression and increase resistance to apoptosis [6,12,14-16,18-21,23]. Mutations in the inhibitor apoptosis protein (IAP-2) gene are observed in lymphomas and lead to a more pronounced inhibitory effect of IAP on caspases, blocking apoptosis [6,12,14-16,18-21,23]. Mutations of the NAIP-1 gene. The NAIP-1 protein belongs to the IAP protein family and is localized in the neurons of the nervous system. Mutations in the gene encoding lead to the development of spinal muscular atrophy associated with the death of neurons in the anterior horns of the spinal cord [6,12,14-16,18-21,23]. Necrosis is a process of cell death, which is characterized by cell swelling (oncosis), violation of the integrity of the plasma membrane, degradation of organelles and DNA [24,16,17]. Necrosis is an irreversible post-mortem change in a cell, consisting in the gradual enzymatic destruction and denaturation of its proteins. It develops with excessive alteration of the cell, does not require energy expenditure and does not depend on regulatory signals of local and central origin. Necrosis is usually established by the destruction of cell membranes using electron microscopy. The causes of violent cell death (necrosis) can be:

- Depriving her of food and oxygen.
- The action of various pathogenic agents leading to irreversible changes in structure and function with inhibition of the most important metabolic processes [24,16,17].

Necrosis is preceded by a deep, partially irreversible stage of cell damage - necrobiosis. Despite the variety of etiological factors that provoke the development of necrobiosis and necrosis, molecular and cellular changes detected during cell death are in most cases of the same type. Allocate hypoxic and free-radical necrobiosis. Hypoxic necrobiosis is initiated by various pathogenic factors that cause prolonged hypoxia. The mechanisms of free-radical cell damage can be triggered without hypoxia, and sometimes even in conditions of excess oxygen. Both types of necrobiosis can be combined and complement each other. Their outcome is damage to the cell, in which it is not capable of independent energy supply and subsequently undergoes necrosis [24,16,15,17].

The Main Differences Between Apoptosis and Necrosis are

- Maintaining the integrity of the cell membrane with an increase in its permeability only for substances of small molecular weight.
- Cell size reduction (cell wrinkling).
- Absence of swelling of cellular organelles.
- Condensation of cytoplasm components, not its lysis.
- The need for energy supply [24,15,20,25,17].

There are two main types of necrosis:

- Coagulation (dry) necrosis, in which acidosis develops in the cell, protein coagulation occurs, calcium accumulation and aggregation of cytoskeletal elements are noted. This type of necrosis is often observed in severe hypoxia, is predominantly noted in tissues rich in protein and calcium and is characterized by early and irreversible damage to mitochondria [16,25].
- Colliquational necrosis, which is characterized by the predominance of hydrolytic processes of lysosomal autolysis or heterolysis with the participation of phagocytes. At the same time, the focus of necrosis is softened, the formation of hydroxyl radicals and endogenous saponification of cells are observed, which leads to the destruction of its structures, including membranes [16,25].
- There are no clear boundaries between coagulation and colliquation types of necrosis [16,25,17].

The information presented in the work on the functional features of cell death will serve as a fundamental basis for further study of destructive processes in cytology with the subsequent implementation of the results obtained into clinical practice.

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