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THE ROLE OF THE DRUG VIFERON® IN THE REGULATION OF APOPTOSIS AND ITS EFFECTIVENESS

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Annotation

The end of the 20th century was marked by advances in biology and medicine, including theoretical immunology, which made it possible to take a new look at the etiopathogenesis of a number of diseases. In particular, this refers to changes in the understanding of innate immunity, the discovery of the interferon system, the identification of immunoregulatory cells and subpopulations of lymphocytes producing opposing cytokines, as well as their role in autoimmune pathology.

Key words

immunity, apoptosis, hyperthermia, interferon, viferon

In recent years, the understanding of the mechanisms of programmed cell death has changed dramatically, making it possible to distinguish apoptosis, necrosis, autophagy, mitotic catastrophe, cellular senescence, and phagocytosis mediated by the presentation of “death signals” on the membrane as independent forms . The phenomenon of apoptosis, discovered relatively recently , is of particular importance. It has been established that the genetic program within the cells of the body, which ensures their life cycle, under certain physiological or pathological conditions, including viral infections, triggers the process of apoptosis (programmed cell death).

Viruses within an infected cell are capable of disrupting cytokine receptor signaling and reducing apoptotic activity, which necessitates the search for ways to regulate and correct apoptosis. The assessment of apoptosis during clinical and immunological examination of patients with various diseases is important for substantiating methods of apoptosis correction, including the use of interferon-based drugs.

Apoptosis is programmed cell death.

Normal development of the organism and functioning of the immune system are maintained by the balance of homeostasis (the ratio between newly formed and dying cells). Apoptosis is an essential tool of morphogenesis and ensures the normal functioning of multicellular systems . This process is regulated by programmed (physiological) cell death. During apoptosis, cell populations are cleared of aged, unwanted, or damaged cells.

The primary morphological features of this refined process include chromatin condensation and cell shrinkage. Subsequently, the cell membrane forms small blebs, and the cell begins to package its contents into vesicles. Some of these vesicles contain fragments of condensed (pyknotic) nuclear material, resulting in the formation of apoptotic bodies, which are engulfed and destroyed by macrophages. No inflammatory response occurs because cytoplasmic enzymes and toxic metabolites remain enclosed within the cell membrane .

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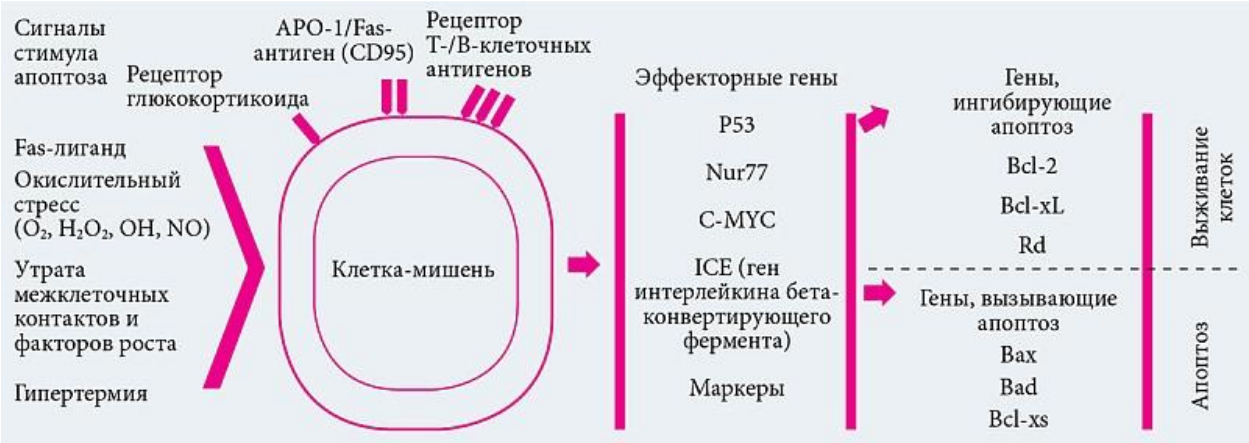
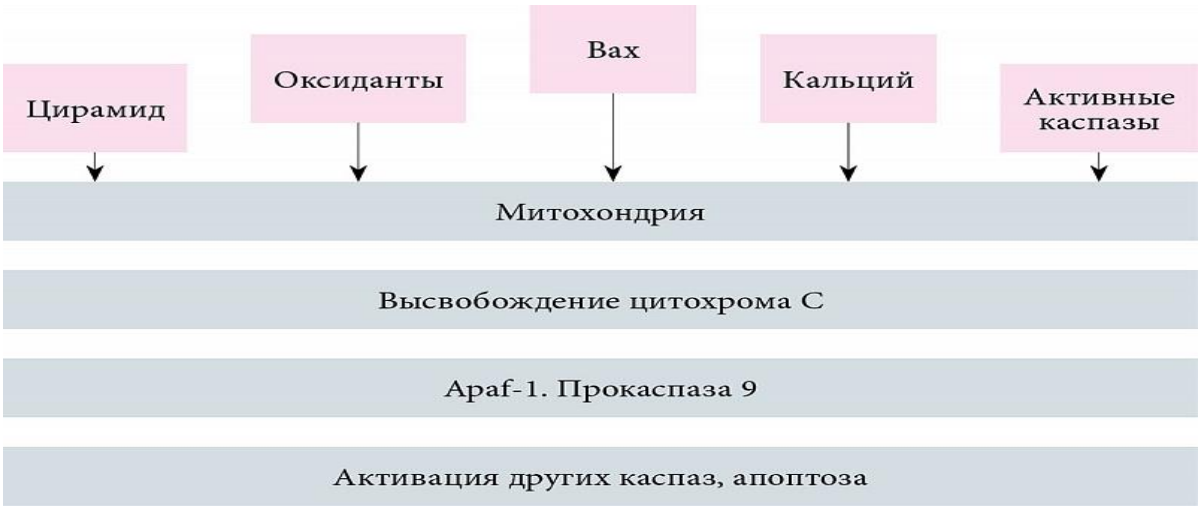


Thus, the structural integrity of biological membranes prevents the release of cytoplasmic contents, including lysosomal enzymes, into the extracellular environment, thereby avoiding structural and functional tissue damage and inflammation during apoptosis.

Apoptosis is a genetically regulated process that requires an energy supply and the synthesis of specific proteins. Cell fragmentation during apoptosis can be stimulated by a range of signals, including physiological stimuli (for example, antigen binding).Regulatory signals include disruption of intercellular contacts, withdrawal of growth factors, hyperthermia, or the action of granzymes. A common intracellular mediator of apoptosis may be oxidative stress (O_2, H_2O_2, NO, OH radicals), which activates nucleases that cleave DNA into fragments



Structures involved in the initiation of apoptosis mechanisms.

Knowledge of apoptosis has made it possible to formulate the concepts of positive and negative activation of immune system cells , which are necessary for assessing their functional state. Positive activation refers to the classical activation of lymphocytes under the influence of specific or nonspecific stimuli, contributing to the realization of the cell's effector functions (cytotoxicity, synthesis of immunoglobulins and cytokines). Positive activation is accompanied by increased expression of activation markers on T- and B-lymphocytes, such as CD25, CD40L, HLA-DR, and others. In negative activation, lymphocytes express the activation marker CD95 (Fas/APO-1) and its ligand FasL. Fas/APO-1 can initiate apoptosis after interaction with FasL.

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Disruption in the expression of Fas receptors and other components of apoptosis leads to the development of autoimmune lymphoproliferative syndrome, manifested by a range of diseases characterized by benign lymphoproliferation, hyperimmunoglobulinemia, and autoimmune disorders.

One of the membrane cell receptors responsible for controlled tissue homeostasis and immune response is the Fas receptor (CD95/APO-1), a protein with a molecular weight of 45 kDa. Its function is associated with the rate of maturation and restoration of the cell pool. In addition to the Fas receptor, another membrane protein, Fas ligand (FasL), is present on the surface of many hematopoietic cells. Fas ligand also exists in a soluble form as a protein with a molecular weight of 1.7×10^4 Da. Surface molecules such as CD95 (APO-1 or Fas antigen) are important mediators of apoptosis. The CD95 molecule belongs to the receptor protein family TNF (tumor necrosis factor) / NGF (nerve growth factor). Upon activation by APO-1/Fas ligands, a cell expressing the CD95 receptor sends an apoptotic signal to other cells bearing this receptor .

There are specialized apoptosis receptors belonging to the TNF family, collectively referred to as death receptors (DR) (DR1–TNF, DR2 – Fas receptor/CD95, DR3, DR4–DR6). Ligands for TNFR1 include TNF and lymphotoxin alpha; for the Fas receptor – the membrane molecule Fas ligand (FasL, CD178); for DR3 – DR3L. Two main receptors are known to receive signals that trigger apoptosis: Fas (CD95) and the type 1 TNF receptor (p55), TNFR1. They contain a “death domain” in the cytoplasm that transmits the death signal into the cell (effector gene ICE). The generation of intracellular apoptotic signals is primarily associated with the p53 protein, which is expressed in the presence of chromosomal damage, DNA breaks, and other genetic abnormalities under various stimuli, especially ionizing radiation. During apoptosis, the cell, remaining in a shrunken state, loses part of its genetic (nuclear) material .

Apoptosis is also accompanied by the activation of a number of genes. One of the most significant is interleukin-1 beta–converting enzyme (ICE). The initial phase of apoptosis is also characterized by increased expression of effector genes such as p53, Nur77, and c-MYC proteins. During apoptosis, in addition to genes that induce it (Bax, Bad, Bcl-xs), genes that inhibit apoptosis are also expressed (Bcl-2 encodes a protein that prevents apoptosis). As a result, both apoptosis regulation and cell survival are genetically controlled. This is particularly important in the pathogenesis of viral infections. Genes that trigger apoptosis ultimately lead to its development .

Pathways of Apoptosis Induction

There are two mechanisms that initiate cell death: the intrinsic (mitochondrial) and the receptor-mediated pathways. Mitochondrial apoptosis develops under conditions of deficiency of survival factors (cytokines and contact signals from neighboring cells), as well as under the influence of cytotoxic agents (radiation, steroid hormones, cytostatics). As a result, the balance of mitochondrial factors of the Bcl-2 family (proapoptotic and antiapoptotic) is altered. Through pores formed in the mitochondrial membrane, cytochrome c is released into the cytosol, where it activates caspase-9 by binding Apaf-1 with ATP/dATP and procaspase-9. Subsequently, apoptosis proceeds with the formation of new caspases and cell destruction. Initiator caspases activate effector caspases.

The receptor-mediated pathway is triggered when ligands bind to membrane receptors on the cell surface. Binding of the Fas receptor with Fas ligand activates apoptosis. Membrane-bound FasL induces apoptosis through direct cell-to-cell contact, whereas soluble FasL is responsible for autocrine or paracrine cell death.

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Both mitochondrial and receptor pathways activate initiator caspases, after which the apoptotic process proceeds through a common pathway involving effector caspases 3, 6, and 7, with caspase-3 playing a central role. These caspases target numerous proteins, many located in the nucleus. One key target is the CAD endonuclease, which causes DNA fragmentation. Cleavage of other targets disrupts the cell cycle, adhesion, and morphology. Particular attention is given to apoptosis mechanisms induced by cytotoxic killer cells. Cytotoxic T-lymphocytes (CD8+) carry out their function either without secretion of lytic enzymes (non-secretory lysis) or through secretory lysis involving lytic enzymes. Antibody-dependent cellular cytotoxicity also contributes via Fc receptor (CD16) interaction. Granzymes, especially granzyme B, activate caspase-10. Fas–FasL interaction activates caspase-8, while TNF-alpha activates caspase-2. All pathways converge on caspase-3. Granzyme B can also directly activate caspases-3 and -7.

Apoptosis induction begins with perforin, which forms pores in the target cell membrane, allowing granzymes to enter and activate caspases, ultimately leading to DNA fragmentation and cell death. This mechanism is crucial in transplant rejection, autoimmune diseases, and elimination of virus-infected or tumor cells.

Apoptotic cells are rapidly eliminated by phagocytosis. This is facilitated by membrane asymmetry and exposure of phosphatidylserine on the cell surface, which is recognized by macrophages. Adhesion molecules and receptors further promote phagocytosis.

The Role of Apoptosis in Normal Body Function

Apoptosis plays a role comparable to cell proliferation and differentiation. It is essential during development and for maintaining cellular homeostasis in adults, especially in hematopoiesis, inflammation, and immune responses. Excess immune cells are eliminated via apoptosis in the absence of survival factors. Antiapoptotic proteins (Bcl-2, Bcl-xL) can prevent this process. Apoptosis also eliminates lymphocytes with defective antigen receptors and plays a key role in both positive and negative selection of T-cells, preventing autoimmune reactions.

Apoptosis is essential for terminating immune responses and regulating immune cell populations. It also underlies cytotoxic activity of NK cells and cytotoxic T-lymphocytes.

Clinical Significance of Apoptosis Testing

Apoptosis assessment is important in cell therapy preparation, drug testing (especially cytostatics), and evaluation of immune deficiencies.

Modern methods include flow cytometry, detection of hypodiploid cells, and early markers such as phosphatidylserine using annexin V. Expression of Fas (CD95) and Bcl-2 is also evaluated to assess apoptosis risk.

Biological Effects of Type I Interferons

Interferon alpha-2 provides antiviral protection by inducing synthesis of interferon-stimulated proteins. Its effects include:

- Broad antiviral activity
- Inhibition of viral replication
- Prolonged antiviral effect

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Interferon alpha is produced by dendritic cells, macrophages, and leukocytes in response to infection. It binds to specific receptors on cell membranes, activating intracellular signaling pathways (JAK–STAT), leading to transcription of antiviral and proapoptotic genes.

It induces apoptosis through:

- TRAIL and death domain pathways
- Proapoptotic proteins (Bak, Bax)
- Activation of caspases

Interferon also enhances immune responses, increases MHC class I expression, activates NK cells, and modulates cytokine production.

Regulation of Apoptosis in Clinical Practice

Viruses can suppress apoptosis and immune responses, promoting persistence. Evaluation of TNF-dependent apoptosis pathways helps in understanding and correcting these нарушения using interferon-based therapies. Studies of chronic viral infections (hepatitis B, C, herpesvirus, CMV, HPV) show altered levels of apoptosis markers such as sFas, TRAIL, and TNF-alpha. Reduced TRAIL and sFas levels, especially in high-risk HPV, indicate impaired apoptosis and viral persistence.Interferon alpha-2b preparations, including Viferon®, enhance apoptosis in infected and tumor cells, partly through increased TNF levels and Fas signaling.

Conclusion

The interferon system plays a significant role in apoptosis regulation. Type I interferons exert antiviral, immunomodulatory, antiproliferative, and proapoptotic effects. Apoptosis is regulated by cytokines and intracellular signaling pathways and can be divided into two phases: signal initiation and execution via caspases. Interferon alpha/beta can both induce and modulate apoptosis. Viferon® acts as a regulator of apoptosis, including inhibition of apoptotic signaling in certain immune cells. Understanding apoptosis mechanisms and their dysregulation is essential for studying disease pathogenesis, diagnosis, and development of new therapies. Incorporating Viferon® into комплексную терапию demonstrates its effectiveness in correcting apoptosis regulation in chronic viral infections, including those with high oncogenic risk.

№ References

1 Mansky, V. K. (2007). Cell death pathways and their biological significance. *Cytology, 49*(11), 909–915.

2 Kerr, J. F., Wyllie, A. H., & Currie, A. R. (1972). Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer, 26*(4), 239–257.

3 Varga, O. Y., & Ryabkov, V. A. (2006). Apoptosis: Concept, mechanisms of implementation, significance. *Human Ecology, 7*, 28–32.

4 Fomchenko, N. E., & Voropaev, E. V. (2013). Biological aspects of apoptosis (literature review). *Health and Ecology Issues, 1*(35), 39–45.

5 Grigoryev, M. Yu. (2003). Apoptosis in normal and pathology. *Medical Academic Journal, 3*(3), 3–11.

6 Moskaleva, E. Yu., & Severin, S. E. (2006). Possible mechanisms of cell adaptation to damage inducing programmed death. Connection with pathology. *Pathological Physiology and Experimental Therapy, 2*, 2–16.

pISSN:2349-5707 Volume:13,Issue 4, April -2026 eISSN:2349-5715

7 Holoch, P. A., & Griffith, T. S. (2009). TNF-related apoptosis-inducing ligand (TRAIL): A new path to anti-cancer therapies. *European Journal of Pharmacology, 625*(1–3), 63–72.

8 Chervyakova, N. V. (2004). Fas/Fas ligand: Markers of apoptosis. *Laboratory, 2*, 7–9.

9 Khaitov, R. M., Pinegin, B. V., & Yarilin, A. A. (2009). *Clinical immunology manual: Diagnosis of immune system diseases*. Moscow: GEOTAR-Media.

10 Crouse, J., Bedenikovic, G., Wiesel, M., et al. (2014). Type I interferons protect T cells against NK cell attack mediated by the activating receptor NCR1. *Immunity, 40*(6), 961–973.

11 Crouse, J., Xu, H. C., Lang, P. A., & Oxenius, A. (2015). NK cells regulating T cell responses: Mechanisms and outcome. *Trends in Immunology, 36*(1), 49–58.

12 Yarilin, A. A., Nikonova, N. F., Yarilina, A. A., et al. (2000). Apoptosis, its role in pathology and importance of its assessment in clinical immunological examination of patients (review). *Medical Immunology, 2*(1), 7–16.

13 MacMicking, J. D. (2012). Interferon-inducible effector mechanisms in cell-autonomous immunity. *Nature Reviews Immunology, 12*(5), 367–382.

14 De Weerd, N. A., Samarajiwa, S. A., & Hertzog, P. J. (2007). Type I interferon receptors: Biochemistry and biological functions. *Journal of Biological Chemistry, 282*(28), 20053–20057.

15 Isakov, V. A., Arkhipova, E. I., & Isakov, D. V. (2013). *Herpesvirus infections in humans: Guide for physicians*. St. Petersburg: SpetsLit.

16 Sokolova, T. M., Uspelyevsky, G. P., Kolodyazhnaya, L. V., et al. (2011). Effects of interferon inducers on the expression of apoptosis-regulating genes in human lymphocytes. *Cytokines and Inflammation, 10*(2), 75–80.

17 Kharaeva, Z. F., Ivanova, M. R., Kuzmickaya, E. F., et al. (2010). Indicators of activity of TNF-dependent apoptosis pathways in chronic viral infections with high oncogenic risk. *Cytokines and Inflammation, 9*(4), 127–128.

18 Bernardo, A. R., Cosgaya, J. M., Aranda, A., & Jiménez-Lara, A. M. (2013). Synergy between RA and TLR3 promotes type I IFN-dependent apoptosis through upregulation of TRAIL pathway in breast cancer cells. *Cell Death & Disease, 4*, e479.

19 Meylan, E., & Tschopp, J. (2006). Toll-like receptors and RNA helicases: Two parallel ways to trigger antiviral responses. *Molecular Cell, 22*(5), 561–569.

20 Rajasuriar, R., Khoury, G., Kamarulzaman, A., et al. (2013). Persistent immune activation in chronic HIV infection: Do any interventions work? *AIDS, 27*(8), 1199–1208.