ОБЗОР

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REVIEW

АПОПТОЗ В СОСУДИСТОЙ ПАТОЛОГИИ: НАСТОЯЩЕЕ И БУДУЩЕЕ

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В настоящее время роль апоптоза признана при ряде сосудистых заболеваний. Он представляет собой запрограммированную клеточную гибель, которая находится под контролем генетических механизмов и необходима для нормального существования организма. Главной его задачей является уничтожение дефектных или мутантных клеток. Частицы погибших клеток поглощаются макрофагами без развития воспалительной реакции. Апоптоз принимает активное участие в эмбриогенезе, клеточном гемостазе, уничтожении опухолевых клеток. Данный процесс можно разделить на три фазы: сигнальная, эффекторная и деградационная. Его основным компонентом являются цитоплазматические протеазы – каспазы. Каспазы находятся в цитоплазме в неактивном состоянии – в виде прокаспаз. При активации они расщепляются на субъединицы. Белки семейства Bcl-2 являются активными участниками митохондриального пути апоптоза. Они влияют на проницаемость наружной мембраны митохондрий. Нарушения в механизмах апоптоза лежат в основе многих заболеваний, включая ишемические повреждения, аутоиммунные расстройства, злокачественные новообразования. Способность влиять на выживаемость или смерть клетки известна своим огромным терапевтическим потенциалом. В настоящее время активно развиваются исследования, направленные на изучение сигнальных путей, которые контролируют клеточный цикл и апоптоз. В статье обобщены механизмы, участвующие в гибели эндотелия сосудистой стенки и гладкомышечных клеток, а также рассмотрена потенциальная роль апоптоза при атеросклерозе.

Ключевые слова: *апоптоз; эндотелиальные клетки; рестеноз; атеросклеротическая бляшка; гладкомышечные клетки.*

APOPTOSIS IN VASCULAR PATHOLOGY: PRESENT AND FUTURE

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Apoptosis is recognized as a programmed cell death controlled by genetic mechanisms and required for normal existence of an organism. Its main task is elimination of defective or mutant cells. The particles of dead cells are engulfed by macrophages with no development of inflammatory reaction. Apoptosis actively participates in embryogenesis, cellular homeostasis, elimination of tumor cells, and may be divided to three phases: signal, effector, and degradation. Its main components are cytoplasmic proteases – caspases. Caspases exist in the cytoplasm in inactive condition – in the form pf procaspases. Being activated, they break down to subunits. Proteins of Bcl-2 family are active participants of the mitochondrial pathway of apoptosis. They influence permeability of the outer membrane of mitochondria. Disorders in the mechanisms of apoptosis underlie many diseases including ischemic lesions, autoimmune disorders, malignant neoplasms. The ability to influence survival or death of cell is known to possess enormous therapeutic potential. At present, active

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research is under way to study signal pathways that control cell cycle and apoptosis. The article discusses the mechanisms participating in death of vascular endothelium and smooth muscle cells, potential role of apoptosis in atherosclerosis is also described.

Keywords: *apoptosis; endothelial cells; restenosis; atherosclerotic plaque; smooth muscle cells.*

The scientists have long observed the death of cells of the vascular wall in the absence of evident necrosis [1]. In 1972 J.F. Kerr et al. described a new form of cell death different from necrosis that they called 'apoptosis' (translated from ancient Greek as 'leaf fall') [2]. This is a programmed cell death controlled by genetic mechanisms and necessary for normal existence of an organism. Its main role is maintenance of constant cell composition and elimination of defective cells [3]. Disorders in the mechanisms of cell death form the basis for many diseases including ischemic lesions, autoimmune disorders, malignant neoplasms.

Molecular Mechanisms of Apoptosis

Apoptosis may be activated through a system of internal signals. Cells trigger the internal program of self-destruction in response to alteration of hemodynamic parameters or to loss of contact with neighboring cells. On the other hand, apoptosis may be initiated through the external stimuli, such as cytokines, hormones, oxidized lipids, ionizing or viral agents in which case the process takes a more acute and massive character. Some pathways of cell death are associated with multiple cells (for example, those associated with radiation lesion of DNA), while others occur only in particular cells ensuring their effective removal. The proportion between proapoptotic and antiapoptotic molecules determines the destiny of a cell at a particular moment of time [4].

There are several main functional stages in a programmed cascade of cell death.

In the *phase of initiation*, or *signaling*, cells receive inducing signals via attachment of certain molecules ((such as tumor necrosis factor α (TNF-α), Fas-ligand)) to the death receptors (TNFR1, Fas) on the surface of cell with subsequent assembly of death domain-associated proteins (for example, FADD) with resultant activation of caspase-8 [5].

In the *control*, or *effector phase*, activation of caspases takes place with loss of mitochondrial membrane potential. Caspases are a family of cysteine proteases that participate in transduction and realization of the apoptotic program. They exist as inactive pro-enzymes activated by proteolytic cleavage. In central transitions of the apoptosis pathway, caspases 3, 8 and 9 are located.

Effector phase is controlled by Bcl-2 family of proteins which inhibit liberation of cytochrome C or of the apoptosis-inducing factor from mitochondria. Bcl-2 protein family includes both inhibitors (Bcl-2, Bcl-xL and others), and inductors (Bcl-xS, Bax, Bid, Bad, Bak and others) of death [6]. The proportion between antiapoptotic and proapoptotic proteins determines whether the cell will undergo death or not. After receiving a respective signal, Bax or Bak undergo conformational changes and move to the mitochondrial membrane where they induce release of cytochrome C to the cytosol [7].

Phase of degradation of genomic DNA leads to irreversible loss of viability of the cell.

In the *phase of recognition* the dead cell are removed from tissue as a result of phagocytosis by the neighboring cells using different mechanisms (for example, through phosphatidyl serine, PS, or receptor of vitronectin) [8].

Apoptosis of Endothelial Cells

Endothelium of the vessel wall participates in different physiological processes; therefore its death may present the initial stage of pathological conditions. Cell-to-cell contacts are necessary for maintenance and preservation of the endothelial cells, and their loss leads to activation of death program.

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Extracellular matrix may generate signals that suppress p53-controlled pathway of apoptosis. For example, interaction with proteins of the extracellular matrix through αvβ3 integrin inhibits the activity of p53, decreases the level of Bax and activates NF-κB pathway, that promotes survival of cells. Another mechanism consists in activation of the antiapoptotic pathway through stimulation of the activity of proteins of Bcl-2 family. Growth factors (VEGF) inhibit death of cells in response to different stimuli, such as TNF-α, and destruction of the extracellular matrix occurs. This is due to stimulation of the signal pathway of protein kinase C or PI3K-Akt, or due to activation of Bcl-2 antiapoptotic proteins [9].

Fibroblast growth factor (FGF-2) is one of the factors associated with protection of endothelial cells. The study of A. Karsan et al. (1997) showed that FGF-2 specifically induces Bcl-2, but no other proteins of Bcl family. However, other non-Bcl-2 dependent mechanisms, such as phosphorylation of tyrosine, may also inhibit death of endothelium with the help of FGF-2 [10].

Cells of vascular endothelium are permanently exposed to certain hemodynamic forces, whichhave a great effect on their cellular structure and function [11]. NO metabolites released in response to shear stress inhibit activation of caspase-3 and prevent cell death [12,13]. Both suppression of apoptosis and activation of caspase-3 by physiological levels of shear stress may be prevented by pharmacological inhibition of NO synthase [14].

Incubation of endothelial cells with TNF-α noticeably enhances apoptosis through activation of caspase-3. This process can be completely reversed by caspase inhibitors [15]. On the other hand, TNF-α is capable of inducing proteins of Bcl-2 family, and also of activating NF-κB pathway. So, TNF-α can induce both proapoptotic and antiapoptotic pathways [16]. Bcl-2 and Bcl-XL proteins can suppress activation of endothelial cells through specific inhibition of NF-κB pathway, whichshows that these proteins have cytoprotective effects that counteract inflammatory stimuli. Interestingly, interleukin-10 (IL-10) possesses antiapoptotic effect, therefore the balance between survival and death of cells may depend on the balance between pro-and antiinflammatory cytokines.

Apoptosis of Smooth Muscle Cells

After implementation of numerous research works, growth of smooth muscle cells (SMCs) is considered to be the result of opposite effects of cell proliferation and apoptosis. Many growth factors associated with SMCs act as mitogens partially preventing apoptosis and maintaining secretion of Bcl-2 proteins. For example, IGF-I stimulates enhanced expression of inactive phosphorylated form of Bad through P13-kinase dependent pathway. Growth factors and their respective receptors are synthesized in many vascular diseases and may prevent apoptosis of SMCs within the arterial wall [17].

Mechanical factors. M.J. Pollman, et al. (1999) showed that percutaneous transluminal balloon angioplasty (PTA) induces a rapid death of SMCs within the normal arterial wall [18]. Apoptosis of SMCs is associated with activation of stress-activated protein kinase, and introduction of antioxidants causes its inhibition. This signal pathway cannot be activated in neointimal SMCs due to activation of Bcl-xl in them [19]. Oxidized low density lipoproteins (LDLP) promote apoptosis of SMCs partially by suppression of Bcl-2 and activation of caspase-3.

Vasoactive Substances. Local production of high levels of NO in the arterial wall inhibits growth of cells and formation of neointima after PTA [19]. In its turn, angiotensin II (AT II) in the vessel wall facilitates growth of SMCs and thickening of the wall [20]. NO-induced apoptosis is prevented by inhibition of cGMP-dependent protein kinase Iα, and also by addition of AT II. Proapoptotic effect of NO manifests itself at the supraphysiological (pathological or inflammatory) level, and its antiapoptotic effect is observed with physiological (endothelial) concentrations [21]. Similarly, AT II prevents death of SMCs through stimulation of AT1 receptor, but promotes apoptosis through stimulation of AT2 receptor [22].

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Oncogenes and suppressor genes of tumors. C-myc oncogene is expressed in SMCs of atherosclerotic plaques, and these cells demonstrate a lower growth rate as compare to SMCs obtained from the wall of normal arteries. T. Jacob, et al. (2012) proved in their work that SMCs of ASPs are hypersensitive to p53-mediated apoptosis. Activation of p53 temporarily enhances surface expression of Fas and sensitizes the cell to death [23].

Apoptosis in Atherosclerosis

Development of atherosclerotic plaques is associated both with death and proliferation of cells. At present, evidence is obtained of existence of apoptosis in all cells of a plaque: SMCs, macrophages, lymphocytes and endothelial cells. Apoptosis is most common in macrophages, which suggests participation of these cells in its induction. Programmed cell death is almost not detected in normal arteries, is hardly detected in fat streaks and is more common in diffused atherosclerotic lesions [24]. SMCs die in atherosclerotic plaques despite the presence of growth factors. This is associated with expression of c-myc oncogene in the absence of Bcl-2 proteins and with enhanced sensitivity to p53 [25]. Recent data showed enhanced activity of proapoptotic Bax protein in human fat and in atherosclerotic plaques. Bax was not detected in normal arteries with predominating expression of Bcl-xl protein. The balance between pro- and antiapoptotic proteins in atherosclerosis favors the former and implies programming of SMCs to death in the presence of additional proapoptotic stimuli [26].

Apoptosis plays a double role in development of atherosclerosis. Death of SMCs may weaken the fibrous coating of the plaque through reduction of synthesis of the extracellular matrix, which leads to its rupture. On the other hand, the death of macrophages weakens the inflammatory response, reduces synthesis of metalloproteinases with subsequent destruction of the extracellular matrix, which ultimately promotes stabilization of the plaque. The level of cell death in the plaque is 2-10%, and the level of proliferation is less than 1%. Apoptosis is associated with natural progression of atherosclerotic lesions through development of a lipid 'necrotic' nucleus. Death of macrophages is often identified along the edges of the lipid nucleus, which suggests that it may actively facilitate its formation. Elimination of apoptotic cells from an ASP may be ineffective since they compete with LDLP for being eliminated by macrophages. Non-eliminated cells undergo secondary necrosis, which evokes inflammatory response.

One of the main roles of apoptosis in atherosclerosis is associated with its procoagulant potential. Exposure of the cell surface to phosphatidyl serine significantly enhances the activity of tissue factor, which determines thrombogenicity of atherosclerotic plaques and provokes acute ischemic events [27].

Therapeutic Modulation of Apoptosis in Atherosclerosis

M.J. Pollman, et al. (1998) reported regression of a plaque in rabbits after inhibition of Bcl-xl expression through anti-sense oligonucleotide with subsequent induction of the apoptosis of neointima [28].

NO is a potent antiapoptotic molecule for endothelial cells. B.Y. Wang, et al. (1999) also watched regression of atheromatous lesions in rabbits after introduction of L-arginine for induction of apoptosis of macrophages through NO synthesis [29]. On the other hand, it may be dangerous to induce mass death of cells of atherosclerotic lesions without anticoagulant therapy, taking into account their prothrombogenic potential. Dying endothelial cells are mostly localized in the poststenotic area with low shear stress. Consequently, delivery of NO with addition of L-arginine or delivery of endothelial growth factors may restrict death, thrombosis of cells and change the progress of atherosclerosis [30].

Antagonists of AT II receptors and blockers of calcium channels are strong inductors of apoptosis. Antioxidants such as trimetazidine, probucol, C and E vitamins inhibit apoptosis of SMCs after surgical intervention [31,32]. Application of this group of drugs is not sufficiently present in the literature, and the obtained results are contradictory.

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Finally, initiation of cell death in atherosclerotic plaques strongly depends on inflammatory balance. Introduction of IL-10 may be a reasonable strategy to reduce the inflammatory reaction, apoptotic cell death and, consequently, stabilization of the plaque.

Apoptosis and Restenosis

In different atherosclerotic and restenotic lesions 2-50% of cells undergo apoptosis. The models of formation of neointima after PTA in different animals have shown that in the process of recovery, apoptosis occurs at different moments of time and at different levels.

H. Perlman, et al. (1997) showed that death of SMCs is observed as early as 30 minutes after PTBA and is linked with reduction of Bcl-x protein. After that the second wave of apoptosis was observed associated with enhanced proliferation of SMCs [33]. Death of cells in later stages, in the absence of proliferation, participates in regulation of the thickening of intima.

J.M. Isner, et al. (1995) showed a higher rate of apoptosis in restenotic lesions as compared to the primary atherosclerosis of the coronary arteries [34]. However, this conclusion was argued by G. Bauriedel, et al. (1998), who observed reduction of the level of apoptosis in the zone of restenosis. A high cell density is a key finding in late restenosis in the region of the surgery and agrees with the paradigm of the lower parameters of apoptosis leading to hyperplasia. This corresponds with detection of decreased activity of p53 in the restenotic material of coronary arteries [35].

R. Shibata, et al. (2003) noted that PTBA led to insignificant increase in Bax protein and to significant increase in the level of Bcl-xl in 14 days after surgery. The use of Rho-kinase inhibitor in this study induced neointimal apoptosis of SMCs due to activation of Bax, which led to reduction of neointima formation [36].

P. Krishnan, et al. (2019) in their work studied restenotic lesions after the use of a drug-coated balloon during PTA. Lesions in this case were characterized by a significantly reduced number of cells in neointima, SMCs, fibroblast density, by increased activity of caspase-3 and by detection of deposits of type III collagen, in comparison with lesions in case of using the balloons without coating [37].

Conclusion

Further study of death and proliferation of cells is required to develop interventions that could prevent initiation of different diseases.

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