Molecular Markers of Caspase-Dependent and Mitochondrial Apoptosis: Role in the Development of Pathology and Cellular Senescence

A. S. Dyatlova, A. V. Dudkov, N. S. Linkova, and V. Kh. Khavinson

Abstract—The data on the molecular mechanisms of normal and pathological apoptosis are summarized. Three phases of apoptosis are distinguished: signal, effector, and degradation. The signal phase includes the extrinsic (caspase-dependent) and extrinsic (mitochondrial) pathways. Molecular markers of extrinsic and extrinsic apoptotic pathways play an important role in the diagnostics and treatment of immune, bronchopulmonary, excretory, and cardiovascular system pathologies, oncology, and senescence. This review considers the initiator caspases -8 and -9 and the effector caspase-3 as the molecular markers of the caspase-dependent apoptosis. The main molecular markers of the mitochondrial (or caspase-independent) apoptosis are p53, p21, and p16 proteins, which respond to DNA damage and are involved in cellular senescence, as well as chaperon prohibitin and flavoprotein apoptosis-inducing factor.

Keywords: caspase-dependent apoptosis, mitochondrial apoptosis, cellular senescence, molecular markers

INTRODUCTION

The development of medicine is currently characterized by research on the mechanisms of the development of pathological processes at the molecular level. In particular, the phenomenon of apoptosis (programmed cell death) is actively studied. Despite the large number of studies of the molecular mechanisms of apoptosis, the relationship between the disruption of apoptotic processes and the occurrence of many diseases (including cancer) remains unclear (Ryzhov and Novikov, 2002).

The concept of apoptosis was first proposed in 1972. It referred to normal cell death during tissue development and their renewal in adult organisms (Kerr et al., 1972, p. 239). In this definition, it is important that apoptosis is a normal physiological process.

Apoptosis plays a key role in morphogenetic processes and regulation of the cell number in the course of ontogeny of a multicellular organism.

Apoptotic processes are triggered in various pathological conditions, as well as aging, and lead to the death of cells, the survival of which is undesirable for the organism (Rizhov and Novikov, 2002). Apoptosis includes three phases—signal (inducer) phase, effector phase, and degradation (destruction) (Baryshnikov and Shishkin, 2002).

The signaling phase of apoptosis can be implemented via two pathways: extrinsic (involving the cell-death receptors (the caspase-dependent pathway), Fig. 1) and intrinsic (involving mitochondria, Fig 2) apoptosis.

In the extrinsic pathway, apoptotic reactions are triggered by hypoxia, damage by physical or chemical agents, cell-cycle signaling disruption, etc. Apoptosis involving cell-death receptors is characteristic of the immune system (Lewin, 2011).

Cell-death receptors belong to the superfamily of tumor necrosis factor receptors (TNFRs) and include the Fas-type receptors (CD95 and APO-1), TNFRI-type receptors (p55 and CD120A), and additional receptors CARI, DR3, DR4, and DR5 (Gordeeva et al., 2004). All of these receptors are transmembrane proteins, the extracellular domains of which interact with the respective ligand—extracellular death protein (FasL for the Fas receptor, TNF for the TNFR1 receptor, etc). The cytoplasmic domain is a sequence comprised of 80 amino acid residues, which is called the death domain (DD). The apoptotic cascade involves an intracellular adapter specific to each receptor type. For example, the adapter for Fas-type
MOLECULAR MARKERS OF APOPTOTIC PROCESSES

The expression level of certain molecules involved in apoptosis changes in pathology and with aging of the body, which allows their use as molecular markers of various diseases. For example, the p53 marker is used to diagnose cancer and cellular aging, and caspase-3 is used to study diseases of the cardiovascular system. Initiator caspases -8 and -9 are markers of apoptotic activity of lymphoid cells, and prohibitin and flavoprotein AIF can be used to diagnose renal failure.

Caspases -3, -8, and -9: Role in Immunopathology, Tumorigenesis, Endothelial Dysfunction, and Pathology of the Bronchopulmonary and Excretory Systems

Caspases are a family of evolutionarily conserved cysteine proteases that cleave peptide bonds formed by aspartic acid. Initiator and effector caspases are distinguished. The former include caspases -8, -9, -10, and -12. After activation, they affect the effector caspases -3, -6, -7, and -14 (Shirokova, 2007).

Caspases are present in the cell in the form of inactive monomeric precursors, which are activated as a result of proenzyme cleavage and subsequent dimerization. The mechanisms of the assembly of var-
ious caspases differ and depend on the type of the adapter protein that interacts with the procaspase (McIlwain et al., 2013).

Caspases can activate each other, thus forming a caspase cascade. As described above, the caspase cascade can be initiated by two different pathways. In the first case, the cell receives an external signal from the plasma membrane, with caspases -8 and -10 functioning as initiator caspases. In the second case, DNA damage is the signal, and caspase-9 functions as an initiator caspase. Regardless of the pathway that triggers the cascade, its effector caspase is caspase-3 (Maiboroda, 2013).

Caspase-8 is a classic initiator caspase involved in the signal transduction from all types of cell-death receptors (Martynova, 2003). The formation of the FasL–Fas–FADD–procaspase-8 apoptosome causes the autocatalytic activation of caspase-8 (Samuilov et al., 2000). The activated caspase-8 can initiate apoptosis by two pathways. The first is the direct activation of the effector caspase-3. In the second, the bypass pathway is triggered when the level of caspase-8 in the apoptosome is insufficient for the activation of caspase-3. In this case, caspase-8 cleaves the Bcl-2 family protein Bid, which leads to a release of cytochrome c from the mitochondria and triggers the mitochondrial apoptotic pathway (Varga and Ryabkov, 2006). Thus, the Bid protein is the link between the extrinsic and intrinsic pathways of apoptotic signal transduction (Fig. 3).

The key role of caspase-8 in the formation of immunity was shown in a study of transgenic mice carrying a mutation in the CASP8 gene that deactivates caspase-8 (Salmena et al., 2003). The mutation was limited to the population of T cells. The experimental mice were characterized by a decrease in the number of peripheral T cells compared to the control group and the disturbance of the T-cell response to activatory stimuli, which led to the development of immunodeficiency states.

It was shown that initiator caspases -8 and -9 and effector caspase-3 are involved in the ganglioside-mediated apoptosis of T cells. The GBM ganglioside activates initiator caspases -8 and -9 and effector caspase-3 in T cells, thereby inducing apoptotic processes. Inhibitors of caspases -8 and -9 effectively blocked apoptosis, reducing its activity in 60% of cases (Mahata et al., 2015).

In the bronchial epithelium, interaction between the immunostimulant poly-inosinic:polycytidylic acid (polyI:C), which is used to mimic viral infections, and Toll-like receptor leads to the activation of apoptotic processes via the induction of caspase-8 (Koizumi et al., 2016). However, studies of the effect of cigarette smoke on the apoptotic processes in the bronchial epithelium showed that inhibitors of caspases -3 and -9 cannot prevent apoptosis in bronchial tissue, which indicates that these molecules play a minor role in cell death induced by an apoptotic signal such as cigarette smoke (Bucchieri et al., 2015). However, there is evidence that the aeroallergen Der p2, which is produced
by the dust mites *Dermatophagoides pteronyssinus* and causes airway hyperresponsiveness and asthma, induces apoptosis of bronchop epithelial cells by activating both the intrinsic and extrinsic pathways. Recombinant Der p2 increases the cytoplasmic cytochrome *c* concentration, which leads to an increase in the concentration of the active initiator caspase-9 and then the effector caspase-3 (Lin et al., 2015).

The apoptotic processes in acute renal failure (ARF) are currently being studied. To simulate ARF, kidney cell cultures were treated with cisplatin, and the apoptotic and autophagic processes induced by this cytotoxic agent were studied (Kaushal and Shah, 2016). It was found that caspase-8 and the Fas—FADD—caspase-8 apoptosome induce autophagic processes by activating the Atg5—Atg12 complex and that caspase-3 induces activation of the Atg4D complex. These findings are suggestive of the cross mechanisms of autophagy and apoptosis in ARF. There is also evidence that the apoptotic effect of caspases -3, -8, and -9 in cells is mediated by the enzyme serum and glucocorticoid-regulated kinase 1 (SGK-1) (Pastore et al., 2016).

It was shown that caspase-3 is involved in the apoptosis of endothelial cells of the human coronary artery induced by homocysteine (a risk factor for the cardiovascular disease). In this case, the degree of caspase-3 activity is directly correlated with the concentration of homocysteine added to the endothelial cell culture. In the homocysteine-induced apoptosis, the activity of caspase-3 may be reduced at an increased expression of miR-30b microRNA (Li F. et al., 2015). In the vascular endothelium, the apoptotic activity of caspase-3 may be reduced under the influence of the Elmo1 protein, which promotes changes in the shape of cells, their migration, and phagocytosis, as well as the Dock180 protein, which activates G proteins (Schäker et al., 2015). In the study of endothelial dysfunction as a consequence of diabetes mellitus, it was shown that hyperglycemia induces apoptosis of endothelial cells by the mitochondrial pathway by increasing the concentration of cytoplasmic cytochrome *c* and the activity of caspase-3 (Mishiro et al., 2014).

Interesting studies of apoptotic processes were performed with Burkitt’s lymphoma—a non-Hodgkin’s high-grade lymphoma that emerges from B cells and spreads beyond the lymphatic system. The Gb3 glycan (Galα1–4Galβ1–4Glc), which specifically binds to the MytiLec lectin (mussel R-type lectin), is located on the surface of Burkitt’s lymphoma cells. This interaction triggers apoptosis of lymphoid cells by the extrinsic pathway, inducing the expression of TNF-α and its interaction with the cell–death receptors, as well as via the mitochondrial pathway, increasing the activity of caspases -3 and -9 (Hasan et al., 2015). According to other data, the antiproliferative agent icarin, which inhibits tumor activity in some human tumors, can be used as an inducer of apoptosis of Burkitt’s lymphoma cells (and a possible therapeutic agent). Icaritin potentiates the activity of caspases -8 and -9, thus increasing the apoptotic activity of lymphoid cells (Li Z. et al., 2014).

Thus, the initiator caspases -8 and -9 and the effector caspase-3 are actively studied as therapeutic targets in neoplastic diseases, when it is necessary to trigger apoptotic processes and increase their activity. In addition, the expression of caspases -3, -8, and -9 is an
indicator of the cytotoxicity of apoptotic stimuli, which determines the importance of these markers for the studies of apoptotic processes.

Proteins p53, p21, and p16: Role in Immunopathology, Tumorigenesis, Endothelial dysfunction, and Excretory System Diseases

The p53 protein, a product of the TP53 tumor suppressor gene, is a transcription factor that regulates the cell cycle. Activation of p53 leads to cell-cycle arrest and the replication of damaged DNA. In addition to direct DNA damage, p53 is activated in response to a decrease in the concentration of free ribonucleotides, hypoxia, heat shock, high concentration of nitrogen monoxide, and ionizing radiation (Read and Strachan, 1999).

Figure 4 shows the scheme of activation and implementation of the biological functions of the p53 protein.

Under normal conditions, cells express the Mdm2 protein (mouse double minute 2 homolog, also known as E3 ubiquitin ligase). In the absence of DNA damage, its N-terminal domain is bound to the N-terminal domain of the p53 protein, thus preventing the formation of the active form of p53. In response to stress stimuli, the Mdm2:p53 complex is degraded, which leads to a rapid accumulation of active p53. This stimulates mdm2 gene expression by the negative feedback mechanism. The activated p53 migrates from the cytoplasm into the nucleus, where it regulates the transcription of target genes. This results either in the cessation of cell division to begin DNA repair or the triggering of apoptosis in order to eliminate the cells with mutant genome (Gubskii, 2015; Eleftheriadis et al., 2015).

It was shown that p53 is expressed in phytohemagglutinin-activated T cells and promotes their haemostasis (Nagy et al., 2009). According to the studies by Madapura et al. (2016), the activation of p53 in T cells is mediated by Myc and p14ARF proteins. Mutations in the MYC or p14ARF genes, which encode these proteins, disrupt the mechanisms of p53 activation through Mdm2 and cause neoplastic diseases. It was assumed that p53 expression in T cells is regulated by the Wip1 phosphatase to maintain the functional organization of the thymus as a key organ of the immune system. Wip1 prevents hyperactivation of p53 and p38MAPK pathways in thymic cells (Uyanik et al., 2017). It was found that the apoptosis of T cells in leukemia is triggered by the nucleoside analogs decitabine and zebularine (Ruiz-Magañá et al., 2011) and the antihypertensive drug hydralazine (Ruiz-Magañá et al., 2016). Although all of these compounds affect p53 and increase its activity, decitabine and zebularine trigger the caspase-dependent apoptotic pathway, whereas hydralazine triggers the mitochondrial pathway.

In vascular endothelial cells, apoptosis induced by an increase in the expression of p53 increase the expression of the transforming growth factor β1 (TGF-β1), which leads to the accumulation of neointimal smooth muscle cells (Li J. et al., 2015). It was shown that, p53-induced apoptosis in the proximal renal tubular epithelial cells is caused by chronic exposure to cadmium, which inhibits the ubiquitin-conjugating enzyme gene expression. The mechanism of p53-induced apoptosis is realized in the vascular endothelium, brain neurons, and astrocytes (Lee et al., 2016).

The p21 protein, an intracellular protein also known as the cyclin-dependent kinase inhibitor 1A (CDKN1A), is a major target of p53 and causes cell-cycle arrest in the G1 phase (Bunz et al., 1998). The p21 protein, together with p53, blocks further DNA lesions by triggering the repair processes (Novik et al., 2005).

It is found that the phenotype of the mice knockout for the Cdkn1a (p21) gene does not differ from that of wild-type mice. The presence of p21 is probably not required for normal growth and development of the organism. However, at the age of 16 months, the mutant mice spontaneously developed tumors (Martín-Caballero, 2001).

At the same time, the p21 protein exerts antiapoptotic activity. The Akt kinase phosphorylates the p21 protein, thereby promoting its release from the nucleus to the cytoplasm. In the cytoplasm, p21 inhibits the activity of procaspase-3, caspase-8, and caspase-10 and promotes cell division by activating cyclin D–CDK4 and cyclin A–CDK1 complexes (Fig. 5) (Dotto, 2000). These data suggest that p21 plays a dual role in the body: the cytoplasmic form can function as an oncoprotector and inhibit apoptosis,
whereas the nuclear form has the opposite effect. A decrease in p21 protein activity leads to an increase in the ability of the organism to regenerate tissues (Bedelbaeva et al., 2010).

It was established that long noncoding RNA-p21 (lincRNA-p21) can suppress cell proliferation and induce apoptosis of vascular smooth muscle cells in atherosclerosis. The inhibition of lincRNA-p21 causes neointimal hyperplasia in vivo in the model of the internal carotid artery damage and disrupts the interaction of p53 target proteins (Wu et al., 2014).

The p21 protein can regulate the proliferation and activity of T cells. Therefore, the regulation of p21 expression can be used to treat autoimmune diseases such as systemic lupus erythematosus (Daszkiewicz et al., 2015).

In the presence of MytiLec (a new lectin obtained from the Mediterranean mussel Mytilus galloprovincialis), p21 causes cell-cycle arrest and production of TNF-α in Burkitt’s lymphoma cells, which entails the activation of apoptosis (Hasan et al., 2015).

The p16 protein is a tumor suppressor that inhibits the cell cycle via inactivation of the cyclin-dependent kinase-2A, which is involved in phosphorylation of the retinoblastoma protein pRb (a tumor-growth suppressor protein, which inhibits the transition to the S phase of the cell cycle and is regulated via phosphorylation of cyclin D1). Inactivation of the cyclin-D-cyclin-dependent complex of kinase-2A causes inactivation of pRb. This blocks the transcription of the regulatory proteins of the cell cycle and leads to the cell-cycle arrest. It was shown that p16 is the primary target in cancer therapy (Liggett and Sidransky, 1998).

The p16 protein is studied for its possible role as a predictor of the human immune system recovery after surgery. The expression level of p16 in peripheral blood T cells in the elderly after coronary bypass surgery was studied to predict the length of hospital stay after surgery (Pustavoitau et al., 2016). It was shown that the expression level of p16 decreases with age. However, no correlation between the p16 expression and the length of hospital stay after the operation was found. That is, the predictive assessment of this parameter should include additional markers of the functional activity of the immune system.

The p16 protein is involved in cellular senescence of proximal renal tubular epithelial cells as a component of the ATF4/p16 signaling pathway (ATF4 is the activating transcription factor 4) during the development of diabetic nephropathy (Liu et al., 2015).

**Prohibitin: Involvement in the Regulation of Apoptosis and in Tumor Progression**

Prohibitin (PHB) is a multifunctional protein involved in the regulation of apoptosis, cell-cycle control, and stabilization of mitochondrial proteins. PHB is located in the inner mitochondrial membrane, where it functions as a chaperone and controls the proteolysis of mitochondrial proteins. PHB is also located in the nucleus, where it modulates DNA tran-
scription, and in the plasma membrane, where it is involved in the transmission of the cell signal from the insulin receptor and the type 1 protease-activated receptor (PAR1) (Chiu et al., 2013; Giannotta et al., 2015). The human genome contains two copies of the phb gene, which encodes two homologous subunits of the PHB complex—PHB1 and PHB2 (van Aken, 2007).

PHB is involved in apoptotic signal transduction by the extrinsic and intrinsic pathways. Mutations in the gene encoding this protein, its posttranslational modifications, or changes in its mitochondrial or nuclear translocation may affect the cellular life cycle (Peng et al., 2015). An increased expression of prohibitin induces cell resistance to various stimuli by the mitochondrial apoptotic pathway, and the phb gene knockdown increases the susceptibility to apoptotic stimuli. PHB2 function disorders induce apoptosis and death of mice in the embryonic period of development (Baris et al., 2011).

In cancer cells, PHB is required for activation of the Ras-mediated signal transduction pathway, which can modulate the survival and migration of cancer cells. It was found that the anticancer drug roca-glamide is able to increase the apoptotic activity in resistant cancer cells by selectively binding to PHB1 and PHB2. This leads to disruption of the binding of PHB to the c-Raf protooncogene enzyme, cell-cycle arrest in the G0/G1 phase, and inactivation of the Raf—MEK—ERK oncogenic signaling pathway. This effect of roca-glamide was shown on Jurkat cells (human T-lymphoblastic leukemia), HeLa cells (human cervical cancer), and AsPC-1 cells (pancreatic cancer) (Yang et al., 2014).

PHB1 also functions as a specific receptor in white adipose tissue vessels. The endothelial cells of mice and human white adipose tissue are rich in PHB1, and the membrane-bound PHB1 receptor is a target for the adipose tissue-specific peptide (Kolonin et al., 2004). By inducing cytochrome c, PHB1 triggers apoptosis of vascular endothelial cells of white adipose tissue in vivo and prevents obesity caused by a high-fat diet. The specific PHB1-receptor complex in white adipose tissue can probably contribute to the induction of apoptosis as a mechanism of treating obesity (Hossen et al., 2013).

PHB phosphorylated at threonine 258 is a potential metastasizing mediator in lung cancer. Stable expression of the modified PHB in the plasma membrane of human lung cancer cells enhances the invasive ability of cancer cells (Ho et al., 2015).

PHB2 inactivation in mouse renal podocytes causes progressive proteinuria and renal failure and leads to hyperphosphorylation of the S6 ribosomal protein (S6RP), a well-known mediator of the mTOR signaling pathway. Inhibition of the insulin/insulin-like growth factor-1 (IGF–1) signaling system prevented S6RP hyperphosphorylation without affecting the structural defect of mitochondria and delayed the renal failure development in animals deficient for PHB2 (Ising et al., 2015).

AIF Protein: Involvement in the Regulation of Mitochondrial Apoptosis and in the Disturbance of Functions of Immune, Bronchopulmonary, and Excretory Systems

AIF is one of proapoptotic factors released from mitochondria. It realizes apoptosis by the mitochondrial (caspase-independent) pathway (Farina et al., 2017).

AIF is a mitochondrial flavoprotein involved in the embryonic development and survival of cardiomyocytes. The mature form of AIF comprises two FAD-binding domains—the NADH-binding domain and the C-terminal domain. It is bound to the inner mitochondrial membrane, where it regulates the activity of the mitochondrial respiratory chain complex (Hansen, 2015). AIF induces cell death in response to oxidative stress, DNA damage, hypoxia, etc. Numerous intracellular stress pathways are eventually reduced to the depolarization and fragmentation of mitochondria and the subsequent release of the apoptogenic AIF form from the mitochondria to the nucleus, where it causes chromatin condensation and DNA fragmentation (Thal et al., 2011).

In mutant mice deficient for the AIF protein, the activity of the multiprotein complex I of the respiratory electron transport chain is reduced as compared to wild-type mice; i.e., AIF deficiency leads to a disruption of oxidative phosphorylation (Klein et al., 2002; Vahsen et al., 2004).

It was shown that the AIF protein expression in human renal tissue in diabetic nephropathy is significantly reduced proportionally to the renal function reduction. Mice with reduced synthesis of the AIF protein showed signs of chronic kidney disease, including proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, and hyperfiltration. The induction of experimental diabetes in these mice resulted in a more severe renal disease than in diabetic wild-type mice. The results of these studies suggest that AIF is involved in the development of renal disease in humans (Coughlan et al., 2016).

Deletion in the aif gene disrupts oxidative phosphorylation in T cells. AIF deficiency causes a decrease in the activity of T cells, reducing their number. It should be noted that CD8+ T cells are more sensitive to mutations in the aif gene than CD4+ T cells. However, a decrease in the AIF protein expression had no effect on the differentiation of thymocytes (Milasta et al., 2016).

In response to DNA damage in bronchial epithelial cells by cigarette smoke, AIF is translocated from mitochondria to the nucleus, where it induces chromatin condensation and apoptotic DNA fragmentation. In addition, cytoplasmic AIF accelerates the release of other proapoptotic proteins—cytochrome c and procaspase-9 (Bucchi et al., 2015).
Molecular Markers of Apoptosis and Cellular Senescence

Along with genetic instability and epigenetic interactions, apoptosis is one of the key mechanisms of organism aging. The most studied markers of cellular senescence at present are proteins p53, p21, and p16.

For example, brain aging is accompanied by a decrease in the expression of the HMGB1 (high mobility group box 1) protein, which ensures a nonhomologous connection of DNA strand ends in lesions. HMGB1 interacts with p53, functioning as a DNA damage sensor. HMGB1 synthesis is p53-dependent; i.e., the decrease in the HMGB1 expression during aging is caused by the decrease in the p53 level in aging neuronal cells (Salmina et al., 2015).

Although the expression level of the p53 protein or its mRNA in cells does not always increase with aging, the degree of its phosphorylation and, hence, the DNA-binding activity often increases. As a result, the level of the p21 protein, the primary target of p53, increases. The p21 protein is responsible for the p53-dependent arrest of cell division. The p53-dependent induction of the p21 gene leads to cellular senescence due to the inhibition of cyclin-dependent protein kinases (the key cell-cycle regulators) and blocks DNA replication (Moskalev, 2009). Cell death due to senescence is also a protective mechanism of their possible transformation into tumor cells (Baker et al., 2011). The p16 protein, like the p21 protein, functions as an inhibitor of cyclin-dependent kinases (Rheinwald et al., 2002). The expression of p16 increases with age in almost all tissues (Krishnamurthy et al., 2004).

CONCLUSIONS

The study of apoptosis is characterized by the description of molecular markers (inducers, receptors, mediators, and effectors) that are involved in cell death. To date, dozens of molecules involved in apoptosis have been described, but the functions of many of them are not well understood.

The best-studied molecular markers of apoptosis are caspases, which trigger and implement the caspase-dependent apoptosis, and the p53 protein, which triggers the mitochondrial apoptosis. Proteins p21 and p16, which are p53 targets and mediate signal transduction during mitochondrial apoptosis, are also actively studied. The proteins prohibitin and flavoprotein AIF also play an important role in the apoptotic processes in mitochondria.

The regulation of cellular senescence via the effect on the p53 protein and its targets p21 and p16 proteins is studied.

The molecular markers of apoptosis (caspases -3, -8, and -9, as well as proteins p53, p21, p16, PHB, and AIF) considered in the review play a major role in the study of pathological processes in the immune, bronchopulmonary, excretory, and cardiovascular systems in oncological diseases. These molecular markers of the extrinsic and intrinsic apoptotic pathways can serve as targets of geroprotectors.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement on the welfare of animals. This article does not contain any studies involving animals performed by any of the authors.

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