

Mitochondrial dysfunction in cancer

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Abstract

Mitochondria are semi-autonomous organelles of eukaryotic cells. They perform crucial functions such as generating most of the cellular energy through the oxidative phosphorylation (OXPHOS) system and some other metabolic processes. In addition, mitochondria are involved in regulation of cell death and reactive oxygen species (ROS) generation. Also, mitochondria play important roles in carcinogenesis via altering energy metabolism, resistance to apoptosis, increase of production of ROS and mtDNA (mitochondrial genome) changes. Studies have suggested that aerobic glycolysis is high in malignant tumors. Probably, it correlates with high glucose intake of cancerous tissues. This observation is contrary to Warburg's theory that the main way of energy generation in cancer cells is non-oxidative glycolysis. Further studies have suggested that in tumor cells both oxidative phosphorylation and glycolysis were active at various rates.

An increase of intracellular oxidative stress induces damage of cellular structure and somatic mutations. Further studies confirmed that permanent activity of oxidative stress and the influence of chronic inflammation damage the healthy neighboring epithelium and may lead to carcinogenesis. For instance, chronic inflammatory bowel disease could be related to high risk of colon adenocarcinoma.

The data have shown a role of ROS generation, mtDNA or nDNA alterations and abnormal apoptotic machinery in endometrial cancer progress. Recent studies suggest that mtDNA mutations might play a potential role in endometrial cancer progress and indicate an increase of mitochondrial biogenesis in this cancer. The investigators suggested that MtCOI and MtND6 alteration has an influence on assembly of respiratory complexes in endometrial cancer.

In many human cancers, there is a deregulation of the balance between cell growth and death. The tumor cells can avoid apoptosis through a loss of balance between anti- and pro-apoptotic proteins, reduced caspase function and impaired death receptor signaling. Over-expression of the anti-apoptotic BCL-2 gene has also been identified in numerous cancers including colon, thyroid, breast and endometrial cancer. Most studies have found low BCL-2 family gene expression, which could be a sign of blocking apoptosis in breast and endometrial cancer. Moreover, BCL-2 gene expression is correlated with the degree of aggressiveness and differentiation in endometrial cancer. As a result, it could be a valuable predictor of disease progression.

Key words: mitochondrion, cancer, oxidative stress, carcinogenesis, defective apoptotic pathways, inflammation.

Mitochondrial structure

Mitochondria are semi-autonomous, oval-shaped organelles of eukaryotic cells. On average, each human cell contains between a hundred and a thousand mitochondria. Cells that have a greater demand for ATP (adenosine-5'-triphosphate) such as hepatic cells, muscular or gastric gland cells and nerve cells contain about 1-2 thousand mitochondria [1-3]. Structurally, mitochondria possess five compartments: the inner and outer membrane, inter-membrane space, cristae and matrix (the region within the inner membrane). The outer membrane contains multiple copies of porin,

which is permeable to small molecules. Larger proteins can enter mitochondria if they bind to translocase proteins of the outer membrane. The inner membrane is impermeable to most molecules. The transfer of molecules requires special membrane transporters. In addition, the inner membrane contains five types of proteins: respiratory chain protein, ATP synthase, protein import machinery, specific transport proteins that regulate metabolite passage into and out of the matrix, and mitochondria fusion and fission protein [1, 2]. The surface area of the inner membrane is compartmentalized into numerous cristae which can affect chemiosmotic function. The matrix is the space inside the

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inner mitochondrial membrane where most of the citric acid cycle activities and fatty acid oxidation take place [4, 5]. Mitochondria perform essential functions in generating most of the cellular energy through the oxidative phosphorylation (OXPHOS) system and important metabolic intermediates in various pathways such as amino acids, fatty acids and carbohydrates. In addition, mitochondria are involved in the regulation of cell death and ROS (reactive oxygen species) generation [6-10].

Also, mitochondria play compelling roles in carcinogenesis via altered energy metabolism, resistance to apoptosis, increased production of ROS and mtDNA (mitochondrial genome) changes [11-14].

Mitochondrial energy metabolism in cancer cells

Under normoxic conditions normally cells rely on aerobic respiration through oxidation of glucose, fatty acids and amino acids. The glucose enters the cell via specific transporters and it is partially oxidized to pyruvate in the cytosol. Subsequently, the pyruvate can enter the mitochondria to fully undergo oxidation through the Krebs cycle and beta oxidation. The final products of tricarboxylic acid are two GTP (guanosine-5'-triphosphate) or ATP (adenosine-5'-triphosphate), six NADH (reduced form of nicotinamide adenine dinucleotide), two fumarate ubiquinol and four carbon dioxide molecules [14]. Aerobic respiration is the most efficient method of energy generation in cells. Nevertheless, under hypoxic conditions energy generation occurs through the cytosolic process. In the glycolysis process glucose is converted to pyruvate, and then pyruvate is reduced to lactate by NADH. This process is less effective than OXPHOS [15].

The first interest in tumor energy metabolism was brought by the work of Otto Warburg. According to Warburg's observations, normal cells use lactic acid fermentation only in anaerobic conditions while cancer cells show an increased level of lactic acid production even under normal oxygen tension. Besides, Warburg proposed a model of defect in the OXPHOS pathway which stimulates the increase of lactic acid fermentation in tumor cells [15, 16]. As a result, malignant cells produce their energy via a glycolytic mechanism rather than through the electron transport chain. Other works have suggested that aerobic glycolysis is high in malignant tumors. Probably, it correlates with high glucose intake of cancerous tissues such as gliomas, meningiomas and sarcomas [16-20]. Further studies have supposed that inside tumor cells both oxidative phosphorylation and glycolysis were active at various rates [21]. For instance, in MCF-7 cells originating from a mammary gland epithelial adenocarcinoma, the contribution of OXPHOS to the total cellular energy is 80% [22].

Anaerobic glycolysis is not a prerequisite of all tumor cells but could be a response to micro-environmental

conditions such as hypoxia which is observed inside the solid tumors or to glucose limitation. Additionally, the glycolysis advantage in cancer cells could be acquired during the highest proliferation. This observation is contrary to Warburg's theory that the main way of energy generation in cancer cells is non-oxidative glycolysis [23].

Oxidative stress

Oxidative stress reflects an imbalance between the production of reactive species (RS) and antioxidant defenses and leads to an increase in cellular levels of RS [24, 25]. Reactive species are chemically reactive molecules including reactive oxygen species (ROS). Examples include superoxide anion, hydrogen peroxide, and hydroxyl radical. Another group of RS consists of reactive nitrogen species (RNS) such as nitric oxide and nitrogen oxide radicals and reactive halogen or sulfur species [24, 26, 27]. The major source of ROS is mitochondria, where they are produced as a consequence of aerobic respiration and OXPHOS. Another endogenous source of reactive oxygen species is their production by neutrophils, eosinophils, macrophages and peroxisomes. ROS could also be produced through an exogenous way including chlorinated compounds, radiation, metal ions, hormone therapy, smoke and ethanol. Physiological roles of ROS include the effect on vascular tonus, platelet adhesion, regulating proliferation, gene transcription and metabolism [25, 28-31]. For instance, one of the RS, hydrogen peroxide (H_2O_2), acts as an important intracellular messenger, and regulates apoptosis and senescence [29, 30].

Reactive oxygen species are eliminated by protective mechanisms, referred to as antioxidants. Antioxidant mechanisms operate through both enzymatic and non-enzymatic mitochondrial components, cellular membrane and extracellular. The mitochondrial enzymatic defenses include manganese-superoxide dismutase (MnSOD2), glutathione peroxidase (GPx), glutathione reductase (GRed), peroxiredoxins, glutaredoxins and proteins such as cytochrome c. The non-enzymatic defenses are reduced glutathione (GSH), and high NAD(P)II/NAD(P) ratio [32]. SOD2 is one of the most effective antioxidant enzymes. It has antitumor activity too. Therefore, over-expression of manganese-superoxide dismutase leads to tumor growth retardation in several cell lines [33, 34]. The cellular membrane antioxidant mechanisms include vitamin E, β -carotene, and coenzyme Q. Thirdly, there is an extracellular mechanism including metal-binding proteins, bilirubin and vitamin C and extracellular forms of glutathione peroxidases and superoxide dismutases [27].

An increase of intracellular oxidative stress induces damage of cellular structure and somatic mutations, leading to cancerous transformation. Moreover, senes-

cence causes an increase of intracellular oxidative stress and a decrease of antioxidants and accumulation of molecular damage in DNA. These processes, nascent as a result of aging, can lead to an increase of the risk of mutagenesis [35-37].

In cancer cells, ROS generation is often increased. This could be the effect of exposure to the hypoxic micro-environment inside the tumor. This increase may contribute to induction of mtDNA alterations. Cells counteract the destructive effects of ROS increase; therefore, they imply genomic instability. For instance, the hydroxyl radical could activate oncogenes or inactivate tumor suppressor genes and prevent DNA repair [28, 38]. MtDNA mutations correlate with the highest level of antioxidant enzymes such as CAT and PRX3 in endometrial cancer. It could be suggested that mtDNA mutations contribute to increased ROS generation, as a result, leading to compensatory antioxidant mechanisms [39].

The studies suggest that secular inflammation could predispose the host to an increased risk of cancers [40]. For instance, chronic inflammatory bowel disease could be related to high risk of colon adenocarcinoma or chronic pancreatitis may lead to an increased risk of pancreatic cancer [41, 42]. Rudolf Virchow was the first to get interested in the influence of chronic inflammation for cancer development. He demonstrated the presence of inflammatory cells within tumors and growth of tumor as a result of maintaining chronic inflammation [43]. Further studies confirmed that the permanent influence of chronic inflammation and activity of oxidative stress damage the healthy neighboring epithelial and stromal cells and they may lead to carcinogenesis. Inflammatory cells produce essential mediators such as cytokines, chemokines and metabolites of arachidonic acid which activate signal transduction cascades. These mediators also induce alterations in transcription factors including nuclear factor kappa B (NF- κ B), signal transducer and activator of transcription 3 (STAT3), hypoxia-inducible factor-1 α (HIF-1 α), activator protein-1 (AP-1), nuclear factor of activated T cells (NFAT) and NF-E2 related factor-2 (Nrf-2). They are directly responsible for activation of oxidative stress responses. These processes can activate genetic and epigenetic alterations such as point mutations in tumor suppressor genes, DNA methylation and post-translational modifications, causing changes in essential cellular pathways leading to cancer development [44, 45]. In addition, the effect of oxidative stress and chronic inflammation may influence the tumor cell transformation, promotion, survival, proliferation, invasion, and metastasis progression, and regulate angiogenesis [46-49]. ROS may cause DNA damage leading to genetic lesions that initiate carcinogenicity. Similarly, inflammatory cells such as neutrophils could also increase DNA damage via activating substances including aromatic amines,

aflatoxins, estrogens, phenols, and polycyclic aromatic hydrocarbons by ROS-dependent mechanisms. ROS and genomic instability can also activate certain signaling pathways and thus they contribute to cancerous proliferation, angiogenesis and metastasis [50-53]. On the other hand, ROS can perform a role of anti-tumorigenic agents through the induction of cellular aging and cell death [54].

Oxidative status has been reported to play a role in NF- κ B regulation. NF- κ B influences the regulation of several genes involved in tumor development [55]. The role of ROS in activation of NF- κ B is still unknown. Some studies suggest that ROS are indirect messengers in activation of NF- κ B by TNF and IL-1. It is reported that TNF and IL-1 suppression leads to downregulation of the expression of active NF- κ B and could inhibit proliferation of lymphoma and myelogenous leukemia cells [56, 57]. Inhibition or activation of NF- κ B is dependent on intensity of oxidative stress [58].

Reactive oxygen species are also reported to enhance tumor invasion and metastasis. Cancerous cells modify their morphology and adhesive mode, losing their normal epithelial polarization and differentiation. Then, these cells increase mobility, changing their phenotype to an invasive phenotype [59]. Oxidative stress can also activate the expression of intercellular adhesion protein-1 (ICAM-1), which regulates the transendothelial migration of neutrophils together with IL-8. It could play a potential role in tumor metastasis [60].

Some investigators report that the increase of expression of the matrix metalloproteinases (MMPs) could correlate with the invasion and metastasis of malignant tumor of different histogenetic origin. One of the MMP subgroups, gelatinase (MMP-2 and -9), plays a critical role in tumor invasion and metastasis. Their activation is high under prolonged oxidative stress [61].

Solid tumors induce an angiogenic response under the influence of stress factors such as hypoxia, nutrient deficiency and ROS. Tumoral angiogenesis is controlled by angiogenic factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) released by tumor and inflammatory cells in response to ROS production [62, 63]. The release of VEGF causes a massive signaling cascade in endothelial cells that leads to an increasing number of blood vessels [64, 65].

Mitochondrial DNA alteration

Mitochondria possess their own genome (mtDNA) which is inherited only through the mother (Fig. 1). The mtDNA is located in the mitochondrial matrix and it is a circular, double-stranded molecule of 16,569 base pairs in length containing 37 genes. These genes encode 13 polypeptides of the enzyme complexes of the electron transport chain, 2 ribosomal ribonucleic acid (rRNA)

molecules (12S, 16S) (2 genes), and transfer tRNA molecules (22 genes) for protein synthesis [66, 67]. In addition, mtDNA includes the displacement loop (D-loop), which is the major control region for replication and transcription of mtDNA. In this region it mutates several hundred times more frequently than other mtDNA regions [68, 69]. High susceptibility of mtDNA to mutation is caused by being in close proximity to ROS generated by OXPHOS, an inefficient repair system, and lack of protective histones and introns. Therefore, mtDNA is more susceptible to alterations than nuclear DNA [7].

So far, we know several germlines and somatic mtDNA mutations that might be associated with various types of cancer. Recent studies suggested that most mtDNA alterations are located in the D-loop region. The D-loop contains the control region for replication and transcription of mtDNA. Therefore, mutations in this region might contribute to increase in the alterations in mtDNA gene expression. Furthermore, mtDNA mutations may cause OXPHOS deregulation and other components of mitochondrial metabolism leading to induction of the oncogenic phenotype [71, 72]. Nevertheless, the direct influence of mtDNA mutations on progression and side-effects of tumorigenesis is still a matter of debate.

Recent mtDNA mutations studies suggest their potential role in endometrial cancer progression and indicate an increase of mitochondrial biogenesis in this cancer. Guerra *et al.* investigated 23 type I endometrial cancer (EC) samples and matched typical hyperplasia for changes in mtDNA and in canonical nuclear genes (PTEN, KRAS, CTNNB1, TP53). All mtDNA alterations found in hyperplasia and EC samples were concurrent with mutations found in oncosuppressors/oncogenes (PTEN, KRAS, CTNNB1, TP53). Nevertheless, mtDNA mutational events occurred more frequently than nuclear mutations in the same cases. It could be indicated that mtDNA changes were first, followed by genetic instability of canonical genes involved in progression from hyperplasia to neoplasia. MtDNA base alterations were found in coding and non-coding regions. The investigators suggested that MtCOI nonsense change and frameshift alteration in MtND6 have an influence on assembly of respiratory complexes in endometrial cancer. They also claimed a correlation between mtDNA alterations and oncogenic histological features in type I endometrial cancer [39].

Liu *et al.* investigated mtDNA mutations in primary endometrial carcinomas, revealing high frequency of mitochondrial genome instability. Most of them were observed in the D-loop region as a hot-spot region for the majority of cancers. One particular alteration, mt-MSI, that frequently occurred in endometrial cancer samples may provide an important tool for endometrial cancer detection [73]. Polymorphisms in endometrial cancer are also mainly located in the D-loop region.

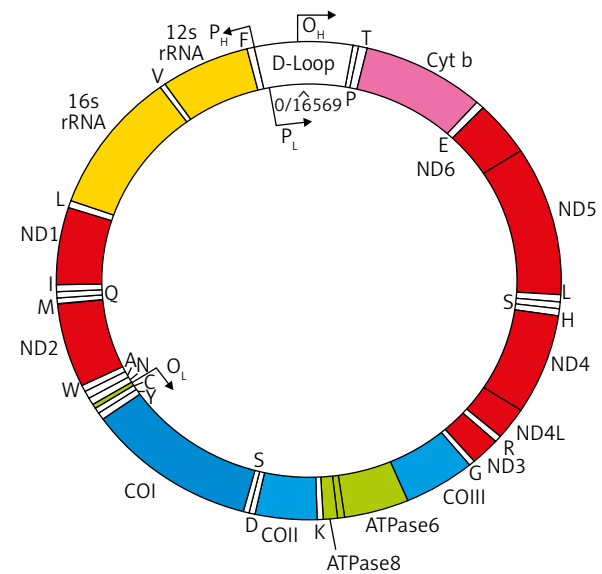


Fig. 1. Mitochondrial genome [70]

The data have suggested specific polymorphisms in the D-loop observed in endometrial cancer such as 16189T>C, 16223C, 207A, and 16126C. Investigators claim that the correlation between polymorphism and endometrial cancer development is high in 16223C/207A genotype. Studies have also suggested the correlation between a specific polymorphism and higher or lower risk of cancer. It is reported that A10398G and T16519C polymorphisms contribute to increased breast cancer risk in European-American females. Conversely, T3197C and G13708A polymorphisms are associated with reduced breast cancer risk in the same group of women [74]. Therefore, mtDNA polymorphism pattern could be useful as a diagnostic marker to select a population at high risk of developing cancer [75, 76].

Furthermore, several factors including estrogens, cigarette smoking, alcohol consumption and caloric intake could induce mitochondrial dysfunction and lead to high risk of breast cancer [77]. The estrogens correlate with breast cancer development through induction of mitochondrial transcription and generation of local ROS during normal metabolism of estradiol [78]. Investigators have also reported that smoking induces increase of mtDNA copy number in response to oxidative damage and could be associated with breast cancer risk [79-81]. Alcohol consumption also correlates with breast cancer development only when it is simultaneously associated with A10398G polymorphism occurrence [82]. Also, life style in combination with type of mtDNA polymorphism might influence cancerous disease development [83].

As mentioned above, mitochondrial DNA alterations have been observed in human cancers. The studies demonstrated that mitochondrial alterations may enable the early detection of cancer, and might contribute to development of a screening system and matching chemo-

or radiotherapy [81, 84-86]. The breast cancer studies have suggested a lower mtDNA content in breast tumor tissues compared to normal cells, which might constitute a biomarker for cancer detection. Interestingly, the same studies have demonstrated an increase of mtDNA copy number in patients with a higher risk of breast cancer. This observation inversely correlates with antioxidant levels, which may suggest increased oxidative stress levels in patients' cells with higher risk of breast cancer. In response to high oxidative stress level mtDNA production is increased [87]. Other data have shown similar dependence in EC between mtDNA mutations and an increase in mtDNA copy number as a compensatory effect [39, 88]. A second marker which is observed in type I EC is a higher mitochondrial mass [39].

Abnormal apoptotic machinery

Apoptosis ensures normal tissue homeostasis by regulation of the balance between cell growth and death. In many human cancers, there is a deregulation of this balance. The tumor cells can avoid apoptosis through a loss of balance between anti- and pro-apoptotic proteins, reduced caspase function and impaired death receptor signaling.

There are three biochemical changes in apoptosis: activation of caspases, DNA and protein breakdown, and changes occurring in membrane recognition by phagocytic cells. In human cells apoptosis is induced via the extrinsic (death receptor) and intrinsic signaling pathway, and the intrinsic endoplasmic reticulum pathway, which is less known. It could be initiated, among others, also via genotoxic, hypoxic, oxidative stress and oncogenic signaling [89, 90].

The best known death receptors are: type 1 TNF receptor (TNFR1 or DR1), Fas (also known as DR2, CD95, APO-1), DR3 (Apo-3), DR4 (also known as TNF-related apoptosis inducing ligand receptor 1 TRAIL-1 or APO2), DR5 (TRAIL-2), DR6, ectodysplasin A receptor (EDAR) and nerve growth factor receptor (NGFR). These receptors possess intracellular death domains (DD) which bind with them, resulting in activation of the signaling cascade [91]. The consequence of some abnormalities in the death receptor or death domains, irrespective of the type of mechanism, is apoptosis dysregulation. For instance, studies suggest a role of reduced expression of APO-1 in the treatment of resistant leukemia and neuroblastoma cells [92, 93]. In addition, loss of Fas and lesion of FasL, DR4, DR5, TRAIL in CIN can contribute to cervical cancer development [94].

Essential components of the intrinsic (mitochondrial) pathway are proteins of the Bcl-2 family. The Bcl-2 family is a heterogeneous group of proteins which may promote or inhibit apoptosis by releasing pro-apoptotic factors such as BAX, BAK, BAD, BID, BCL-Xs, Bik, Bim, Hrk and anti-apoptotic factors (i.e., Bcl-2, Bcl-XL, Bcl-W,

Bfl-1, Mcl-1) [95-97]. Bcl-2 may perform an essential and different role in neogenesis. Overexpression of the anti-apoptotic BCL-2 gene has been identified in numerous cancers including colon, thyroid, breast and endometrial cancer [98-102]. Most studies have found that low BCL-2 family gene expression could be the sign of blocking apoptosis in breast and endometrial cancer [103, 104]. Moreover, BCL-2 gene expression is correlated with the degree of aggressiveness and differentiation in endometrial cancer. Overexpression of Bcl-2 has also been reported to protect prostate cancer cells from apoptosis. Investigators show that overexpression of Bcl-xL could activate multi-drug resistance in cancerous cells. The role of overexpression of Bcl-w was analyzed in colorectal adenocarcinomas as predisposing to progress from adenoma to adenocarcinoma in the colorectal epithelium. In consequence, it could be a valuable predictor of disease progression [104-107].

The third pathway of apoptosis is the intrinsic endoplasmic reticulum pathway. It is initiated by hypoxia, free radicals and glucose starvation. It is dependent on caspase 12 and mitochondrial-independent [90, 108].

As mentioned, caspases 2, 3, 6, 7, 8, 9, 10 play an important role in biochemical changes in apoptosis. It is believed that a low level of caspases or disturbance of their function might lead to damage of apoptosis and result in neogenesis. For instance, a low level of caspase 9 may correlate with poor prognosis in patients with stage II colorectal cancer. Positive and negative roles of caspase 3 have also been documented in carcinogenesis. It was found at a substantially decreased level in ovarian cancer [109-111], while a high level of caspase 3 could be a marker of good prognosis for treatment in lung cancer [112]. Interestingly, increased expression of caspase 3 and caspase 7 could indicate a general deregulation of apoptosis in primary breast cancer. It is unknown whether this damage of apoptosis is a primary or a secondary event in breast cancer [113]. Also, the loss of caspase-1 mRNA and protein was observed in tumor development. This loss was correlated with pTNM stage, lymph node metastasis and poor prognosis in gastric cancer [114].

Alterations of caspase-8 gene expression including missense mutation, stop codon, deletion of leucine 62 and silencing mutations in caspase-9 have been observed in many cancers. For instance, deletion of leucine 62 was found to be associated with the development of vulval squamous carcinoma cells. Another missense mutation (Ala-Val) at caspase-8 codon 96 and silencing mutations in the caspase-9 gene were observed in neuroblastomas, suggesting a lack of caspase-8 expression and potential tumor suppressor role for apical caspase-9 [115-117]. The second group of caspases which is mainly related to cytokine processing during inflammatory processes comprises caspases 1, 4, 5, 13, 14 [109].

Also the inhibitor of apoptosis (IAP) proteins have emerged as an important regulator of inflammation, innate immune signaling downstream and downstream inhibitor of apoptosis. It was reported that IAP proteins and X-linked IAP, XIAP in particular, were demonstrated to inhibit caspase activity [118, 119]. It is believed that IAP members play important roles in the differentiation and proliferation of tumor cells. An increased level of IAP was detected in various human cancer and primary tumor biopsies. Moreover, IAPs are able to act as oncogenes. Accordingly, chromosome amplification of the 11q21-q23 region of c-IAP1 and c-IAP2 was found in many malignant states of cancer and esophageal squamous cell carcinomas [120].

Studies also suggest the occurrence of alterations in apoptotic genes in cancer patients. It was reported that TNF- α gene polymorphisms and a single nucleotide polymorphism (SNP) located in the FAS promoter region were correlated with several cancers. A protective role was detected in the association between DR4 polymorphism and bladder cancer risk and between caspase-8 variant and breast cancer susceptibility [121-125].

One of the most common apoptotic pathways is transcription factor p53, also called tumor protein p53 or TP53 dependent. This protein is encoded by tumor suppressor gene TP53 located at chromosome 17P53, plays a role in promoting transcription of pro-apoptotic factors such as Puma, Noxa, Bax and Apaf 1, and it is also an essential player in processes of development, differentiation, cell cycle regulation, gene amplification, DNA recombination, chromosomal segregation and cellular ageing. It is also called the "guardian of the genome". In response to a spectrum of apoptotic stimuli such as oxidative stress p53 translocates to mitochondria where it displaces anti-apoptotic channel-forming proteins [126-129]. Proteins that hold bad form subunits (PHB) are localized in the inner mitochondrial membrane. The first studies showed a role of PHB as negative cell-cycle regulators, correlation with mitochondrial proliferation and differentiation, and luteolysis in the ovary [130-132]. Subsequent research has suggested a role of PHB in the stabilization of synthesized subunits of mitochondrial respiratory enzymes and also classified it as an anti-apoptotic protein [133, 134]. Furthermore, PHB complex forms (hPhb1p and hPhb2p) are chemically induced in cancerous cells, endometrial hyperplasia and adenocarcinoma, breast cancer cell line and other cancers [135-137]. In cancer patients the PHB may be useful as a clinical marker in therapeutic strategies. In the patient's serum after cisplatin, doxorubicin or methotrexate therapy the PHB level is decreased [138, 139]. The p53 tumor suppressor gene alterations have been correlated with most human cancers, for instance, in melanoma cells where abnormal activity of p53 contributes to the proliferation of these cells [140, 141]. Moreover, low regulation of mutant p53 expres-

sion is effective in reduced cellular colony growth in cancer cells as a result of induction of apoptosis [142].

Disclosure

Authors report no conflicts of interest.

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