JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS
VOLUME 5, ISSUE 06
MONTHLY JOURNALS
ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

THE PARTICIPATION OF MITOCHONDRIA IN THE CONTROL OF THE REDOX STATE OF THE CELL IN THE HUMAN ORGANISM

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ANNOTATION: This article highlights the ongoing scientific research aimed at creating a new generation of cytoprotective drugs that stabilize the membrane of mitochondria, the bioenergetic source of the cell. In this regard, special attention is paid to the correction of mitochondrial disorders, the prevention and development of new approaches to the treatment of age-related hyperlipidemia. Currently, the search for compounds from plants with strong pharmacological activity is an urgent problem worldwide for the development of new approaches to the therapy of various diseases. This is because most synthetic drugs have pronounced side effects, while herbal drugs have low toxicity and are characterized by a relatively mild effect. With the help of these drugs, important information has been obtained about the cellular, mitochondrial and molecular mechanisms of diseases and the most promising targets for their treatment. Today, in our republic, special attention is being paid to developing and improving the effectiveness of methods to strengthen the health of our people and extend their longevity.

KEYWORDS: Cell, NAD/NAD.H, proteins, mRNA, mitochondria, homeostasis redox state, hypoxia, ROS production.

INTRODUCTION: One of the most important conditions for the normal functioning of cells is the homeostasis redox state, i.e. low molecular weight redox components such as oxidized and reduced components (proteins, NAD/NAD.H, flavins, coenzyme Q, reduced and oxidized substrates, etc.).

Mitochondria, which produce superoxide, hydrogen peroxide, nitric oxide, peroxynitrite and other reactive oxygen species (ROS), are actively involved in the regulation of the cellular redox potential and, as a result, affect proteolysis, transcriptional activation, mRNA modification, cellular metabolism and cell differentiation [16; pp. 1371-1374]. An increase in the amount of free radicals in mitochondria causes the development of oxidative stress. Oxidative stress causes oxidative damage to the cell, which often leads to modification of the genetic material [86; pp. 287-290]. Oxidative modification of DNA is the first step in carcinogenesis and aging [90; pp. 757-760]. The imbalance in the redox state caused by oxidative stress is especially characteristic of tumor cells. In many types of cancer, oxidants cause damage at the DNA level, and an increase in such damage indicates the etiology of cancer [61; pp. 126-128; 86; pp. 287-290].

Currently, a new group of anticancer drugs, called "mitokines", has been developed, which are similar to the mitochondria of cancer cells. They destabilize mitochondria and activate the release pathways of proapoptotic proteins (cytochrome c, AIF, Smac/Diablo) in them. Vitamin Y derivatives stand out among the mitokines, the best of which is alpha-tocopherol succinate, a redox neutral substance that kills cancer cells and does not affect normal cells. They interact with complex II of the mitochondrial respiratory chain and cause the production of ROS [27; pp. 13-16]. Interestingly, the "mitochondrial" theory of cancer was first put forward by the German scientist Otto Warburg. He believed that in a cancer cell, the share of glycolysis and OF in the total energy supply is the same (in normal tissues, OF significantly exceeds glycolysis) and drew attention to the fact that damage to ATP synthesis by mitochondria can be the first stage of malignant transformation [94; pp. 1225-1227].

MATERIALS AND METHODS: It has long been assumed that the proliferative properties of the system are related to mitochondrial activity, since mitochondria are powerful oxidants and producers of reduced equivalents. Typically, malignant transformation is accompanied by rapid cell proliferation, and in a number of malignant tumors (most often in glandular tissues, but noted in all tissues) there is a strong proliferation of mitochondria. This phenomenon is called oxyphilia or oncotic transformation. In oncocytoma, mitochondria occupy 90% of the cytoplasm [82; pp. 381-383].

One of the mitochondrial proteins, the peripheral benzodiazepine receptor, is overexpressed in a number of tumors and its expression is associated with the aggressiveness of metastases [55; pp. 2-4]. This protein may perform the function of an oxygen sensor [119; pp. 6408-6410]. A correlation was shown between increased mitochondrial benzodiazepine receptor ligand binding at nanomolar concentrations in tumor cells [99; pp. 2–4] and an increase in the proportion of cells in S phase [123; pp. 364], suggesting the possibility of regulating cell proliferation by regulating the cell cycle. The mitochondrial-localized prohibitins (1 and 2) have been shown to have a wide range of functions, one of which is to inhibit proliferation [137; pp. 1452–1455].

The history of the involvement of mitochondria in the regulation of cell differentiation began with the work of Gerald and co-authors, who showed that rat glial oligodendrocytic precursors are related to the redox status of the cell [74; pp. 781–782]. It turns out that shifting redox systems to a higher oxidation state leads to the development of oligodendrocytes or astrocytes from these precursor cells, while high levels of recovery keep the cells in an undifferentiated state. Various regulatory substances, such as thyroid and other hormones, growth factors, and some chemicals that control cell differentiation, alter the redox state of the cell through mitochondria. The superoxide anion radical has been shown to stimulate osteogenic differentiation of mesenchymal stem cells [117; pp. 225–227]. The proliferative response to PDGF in vascular smooth muscle cells may be mediated by the formation of hydrogen peroxide [100; pp. 411–412].

Mitochondrial function can be regulated by proliferation and phenotype changes, affecting the expression of nuclear genes, as has been shown in myoblasts [116; pp. 2–4].

The involvement of mitochondria in the regulation of organismal development begins in the egg, where mitochondria modulate calcium signals during fertilization [66; pp. 431]. Calcium currents generated by the spermatozoon entering the egg cell membrane are transformed into mitochondrial Sa2+ signals, which stimulate their respiration and general metabolism. Mitochondria also play an important role in the subsequent development of the organism. The expression of mRNA transcription factors stimulates the initiation of differentiation of embryonic stem cells, thereby ensuring their at least partial differentiation into cardiomyocytes [111; pp. 565-566]. In this regard, there are interesting studies showing a connection between the targeted transport of cardiomyocyte mitochondria to progenitor cells and the initiation of differentiation of these cells into cardiomyocytes [102; pp. 2-4; 111; pp. 565-566].

It is known that as a result of the processes occurring in mitochondria, energy is accumulated in cells, and these organelles have all the main functions of an independent organism: contraction, ion transport, heredity, etc. [Alam T.I., Kanki T. et al., 2003; Garrido N., Griparic L. et al., 2003; Kutsiy M.P., Gulyaeva N.A., Kuznetsova Ye.A., Gaziev A.I., 2005; Lipskaya T.Yu., Voinova V.V., 2008]. In addition, mitochondria play a crucial role in apoptosis [Green D.R., Reed J.C., 1998]. The development of many pathological processes, including anoxia, ischemia, hemorrhagic shock, etc., is accompanied by a disruption of the normal functioning of mitochondria and a global loss of mitochondrial function.

RESULTS: Recently, a number of good reviews have been written that analyze in detail the modern ideas about the participation of mitochondria in programmed cell death (apoptosis). The

foundation of these studies was laid by the groundbreaking work of the Kromer and Wang laboratories [Zamzami N., Susin S.A., Marchetti P.et al., 1996], which showed that mitochondria release apoptosis-inducing factor and cytochrome c, which are necessary for the initiation of the terminal stages of apoptosis. The mitochondrial pathway of apoptotic cell degradation "collects" signals from various processes and elements, such as the release of growth factors from the system, damage to the cytoskeleton and DNA, inhibition of macromolecule synthesis, stress state of the reticulum (due to the release of calcium ions from them), and so on [Chipuk J.E., Bouchier-Hayes L., Green D.R., 2006]. In order for the signal coming to the mitochondria from an external source to be amplified by the release of numerous signal molecules in the intermembrane space of the mitochondria, it is necessary to ensure high permeability of the outer mitochondrial membrane.

In particular, when the outer mitochondrial membrane is damaged, cytochrome c leaks from the inner membrane into the intermembrane space, binds to apoptotic protease activation factor in the cytosol, and induces the formation of apoptosomes that activate terminal caspases 9 and 3.

There are two views on the mechanism that ensures the high permeability of the outer mitochondrial membrane. The first of them considers the mitochondria as an osmometer, swelling when all ion gradients are lost and a high content of proteins is preserved in the matrix. Since the surface of the inner membrane is larger than the outer membrane, the swelling of the matrix leads to the alignment of the crystals and, as a result, to the rupture of the outer membrane [Skulachev V.P., 1996].

The second point of view assumes that the specific release of apoptotic factors from the intermembrane space occurs without rupture of the outer mitochondrial membrane. It should be noted that the original outer membrane is highly permeable due to the presence of a voltage-gated anion channel in the open state, allowing the passage of molecules up to 1.5 kDa. The assumption that voltage-gated anion channels can form oligomers of proteins, for example, cytochrome c transport [Zalk R., Israelson A., Garty E.S. et all., 2005] was skeptically accepted by the classical researchers of mitochondrial porins. The oligomerization of proapoptotic proteins with the ability to form giant pores through which cytochrome c can pass is much closer to reality [Antonsson B., Montessuit S., Lauper S. et al., 2000]. The process of outer membrane remobilization is well-organized and is carried out by the proteins of the bc1-2 family, which contain four homologous domains, designated VN1-4, in their structure. Proteins with all four domains exhibit antiapoptotic properties, while proteins with less than four domains exhibit proapoptotic properties [Kuwana T., Newmeyer D.D., 2003].

The proapoptotic protein family can be divided into two subgroups, one of which retains most of the domains (VN 1, 2, 3), and the other retains only the VN 3 domain. It should be noted that only individual multidomain proapoptotic proteins increase the permeability of the outer mitochondrial membrane. This led to the assumption that these proteins are inactive in quiescent non-apoptotic cells [Letai A., Bassik M.C., Walensky L.D. et al., 2002]. This assumption is supported by the presence of a certain amount of proteins and cytochromecat mitochondrial contact sites [Vyssokikh M.Y., Zorova L., Zorov D. et all., 2002; Zorov D.B., Kobrinsky E., Juhaszova M., Sollott S.J., 2004]. It is likely that the contact sites of mitochondria retain the same fraction of cytochrome c that is part of the mitochondrial protein (arrow) that is released during the apoptotic signal transduction.

There are also opinions that nonspecific permeability of the inner membrane is an integral part of the mitochondrial stage of the apoptotic cascade [Isaev N.K., Zorov D.B., Stelmashook E.V. et al., 1996]. In addition, the protein complex of contact sites responsible for the induction of nonspecific permeability is the most important link in the participation of mitochondria in apoptosis [Beutner G., Ruck A., Riede B. et al., 1996]. In in situ experiments, cell death caused

by oxidative stress, resulting from the replacement of hypoxia with normoxia, occurs with the induction of mitochondrial nonspecific permeability [Griffith E.J., Halestrap A.P., 1993]. It is self-evident that in systems where apoptotic death is undesirable (in particular, postmitotic cells such as neurons and cardiomyocytes), the strategy for preventing death should be directed at preventing mitochondrial nonspecific permeability [Juhaszova M., Zorov D.B., Kim S.H. et all., 2004]. The mechanism by which cardiomyocytes are protected from oxidative stress-induced death is still unclear, but it is provided by another recently discovered mitochondrial protein specific for cell gap junctions, connexin-43 [Boengler K., Dodoni G., Rodriguez-Sinovas A. et all., 2005].

It is often difficult to distinguish between the apoptotic and necrotic systems of cell death, but recent data suggest that while apoptosis involves fragmentation of mitochondria and changes in the topology of the inner mitochondrial membrane, this is not the case with cell necrosis.

In addition to the hypothesis of regulation of programmed cell death by mitochondria, assumptions have also been made about the programmed control of their destruction by mitochondria [Zorov D.B., Kobrinsky E., Zhuhaszova M., Sollott S.J., 2004], which is reflected in the concepts of mitoptosis and organismal death (phenoptosis) [Skulachev V.P., 1999].

Recently, a human mDNA mutation has been described, the carrier of which has hypertension, hypercholesterolemia and hypomagnesemia, a cluster of symptoms characteristic of the metabolic syndrome [Wilson F. H., Hariri A., Farhi A. et al., 1994], which is a risk factor in aging.Also in the same studies [Trifunovic A., Wredenberg A., Falkenberg M. et al., 2004; Wilson F. H., Hariri A., Farhi A. et al., 1994] it was suggested that the loss of mitochondrial fractions associated with aging determines the hypertension and hypercholesterolemia that occur during aging.

The discovery of the transglutaminase enzyme [Rodolfo C., Mormone E., Matarrese P. et al., 2004], specifically its TG2 isoform [Krasnikov B.E., Kim S.Y., Mc Conoughey S.J. et al., 2005], which carries the VN3 domain in mitochondria and ensures the assembly of various proteins, further strengthens the view of the role of mitochondria as a powerful regulator of cell death.

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