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The involvement of mitochondrial proteins in tumorigenesis

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Abstract: *Mitochondria are the key organelles for life. Mitochondria are important mediators of tumorigenesis. Mitochondria are key participants in tumorigenesis and development. In-depth study on the role of mitochondria in the survival and growth of tumor cells is not only conducive to our understanding of tumor genesis and development, including oncogene activation, tumor suppressor gene inactivation and other aspects, but also of far-reaching significance in the diagnosis and treatment of tumors.*

Keywords: *mitochondria, tumor, protein*

1. Introduction

Mitochondria are the key organelles in charge of cell life and cell death. Living bodies need to breathe oxygen to survive, and 98% of the oxygen we breathe in is provided to mitochondria [1]. Without mitochondria, oxygen would be of no use to us, and mechanical oxygen delivery from the lungs alone would not make efficient use of oxygen. Without mitochondria, red blood cells, or hemoglobin, the circulatory system's delivery of oxygen to tissues is a futile endeavor. The energy supply of mitochondria is inseparable from the evolution of higher organisms. They are responsible for the production and supply of energy to the body, including muscle contraction of skeletal muscle, cardiac muscle, intestinal smooth muscle, vascular system, etc. [2]. The energy supply of mitochondria maintains ion gradients on both sides of the cell membrane that excitable cells can excite. The basic steps of neurotransmitter synthesis, vesicle loading, exogenesis and fusion in normal life activities all depend on mitochondrial energy supply [3]. Mitochondrial diseases in humans have devastating effects on the body, affecting multiple tissues including the nervous system, heart and muscle[4]. Therefore, mitochondrial dysfunction inevitably leads to disease, starting with subtle changes in tissue function and a small amount of cell death, and eventually leading to severe dysfunction and tissue necrosis.

Many literature reports have suggested that mitochondria are important mediators of tumorigenesis, because the occurrence of tumor requires mitochondria to flexibly adapt to changes in the cell environment. In addition to changes in mitochondrial bioenergetics, they include mitochondrial biogenesis and turnover, fission and fusion dynamics, cell death susceptibility, oxidative stress regulation, energy metabolism and information transmission signaling. Therefore, understanding mitochondrial function and its mechanism during tumorigenesis will be the key to the next generation of cancer therapy. In 1956, Warburg found that cancer cells underwent aerobic glycolysis, which involves the glycolysis of glucose into lactic acid in the presence of oxygen, rather than the complete oxidation of glucose by mitochondrial respiration [5]. This discovery has aroused extensive attention of scholars on the role of mitochondria in tumor genesis.

The main function of mitochondria is to produce ATP, which is necessary for the life of the cell, so it is also called "the energy factory of the cell". However, mitochondria perform many functions beyond energy production, including the generation of reactive oxygen species (ROS), REDOX molecules and metabolites, cell signaling and regulation of cell death and bioanabolism. These functions of mitochondria in normal physiology make them important cellular stress sensors to help cells adapt to their environment. But mitochondria also give tumor cells considerable flexibility to survive and grow in harsh environments, such as nutrient deficiencies, hypoxia and during cancer treatment, so mitochondria are key participants in tumor genesis and development. In fact, mitochondrial biosynthesis is increased in cancer cells. Various signal pathways, changes in cell growth microenvironment and gene mutations related to tumor seem to be inclined to regulate mitochondrial function to promote the occurrence and development of tumor. Changes in mitochondrial function, such as abnormal energy metabolism, structural changes, mitochondrial DNA abnormalities, immune

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evasion, oxidative stress and autophagy disorders, are all involved in tumorigenesis.

Activation of oncogenes and loss of tumor suppressor factors can change the metabolic pattern of tumor cells and induce aerobic glycolysis. Glycolysis pathway provides survival conditions for abnormal proliferation of cancer cells. In addition, excessive calorie intake can increase the risk of cancer, and calorie restriction can reduce oxidative stress. Therefore, the understanding of the multifaceted relationship between metabolism and cancer will help us better search for cancer treatments.

2. Abnormal mitochondrial metabolism

2.1 Changes in mitochondrial glucose utilization

Instead of complete oxidative phosphorylation by mitochondria, many tumors transfer glycolytic intermediates to the phosphoric acid sugar-free pathway and lipid biosynthesis. In some tumours, such changes are achieved by limiting the use of pyruvate by mitochondria. Mitochondrial regulation of pyruvate can be regulated by pyruvate kinase (PKM), which catalyzes the final step of glycolysis to produce pyruvate. Specifically, PKM2 is increased in cancer cells, which can accumulate glycolysis intermediates and be used to synthesize pyruvate [6]. In addition, mitochondrial pyruvate vectors (MPC1 and MPC2) are down-regulated in many cancers [7, 8], and up-regulated MPC can attenuate tumor growth in xenotransplantation models. The presence of aerobic glycolysis in tumor cells does not damage the function of mitochondria and reflects the metabolic flexibility of mitochondria.

2.2 Amino acid metabolism

Glutamine is the most abundant free amino acid in human body, which is the substrate for TCA cyclic oxidation and the starting material for macromolecule synthesis [9]. Most intracellular glutamine is converted to glutamate within the mitochondria by glutaminase. Glutamate can be converted to α -ketoglutaric acid by glutamate dehydrogenase or transamination into the tricarboxylic acid cycle. The amide nitrogen on glutamine is used for nucleotide and amino acid synthesis, and the glutamine derived carbon is used for glutathione, amino acid and lipid synthesis. Glutamine is elevated in many tumors, most of which are caused by c-MYC upregulation of glutaminase [10]. Deletion of the glutaminase allele or participation of glutaminase inhibitors inhibits tumor growth in a variety of mouse cancer models [11]. Upregulation of glutamine synthase and increased glutamine synthesis have been found in some tumors [12,]. In many breast cancer and glioblastoma cell lines, increased glutamine synthase activity and increased glutamine synthesis are beneficial to cell survival and proliferation [14, 15]. The metabolic process from glutamine to α -ketoglutaric acid can be inhibited by tumor inhibitors through SIRT4 (mitochondrial targeted silencing regulator protein). In some lymphoma models, the loss of SIRT4 expression increases the consumption of glutamine and accelerates the occurrence of tumors [16]. In addition, transaminases can use glutamate nitrogen to couple α -ketoglutaric acid to the synthesis of nonessential amino acids, a pathway through which tumor cells can supply their own biosynthesis and maintain REDOX homeostasis. In addition, nucleotide synthesis in mitochondrial carbon metabolism also contributes to tumor development. Mitochondrial enzymes are the main function of synthetic folic acid serine hydroxymethyl transferase (SHMT2) 2 and folinic acid (methylene dehydrogenase (MTHFD2), 2 in human glioblastoma tumor, SHMT2 with ischemic cells of the tumor area adjacent to the high expression, and in ischemia animal model of tumor, the expression of SHMT2 promotes cancer cell survival. MTHFD2 can directly act on SHMT2 to produce formyl-tetrahydrofolic acid. Formyl-tetrahydrofolate promotes the initiation of mitochondrial translation, producing mitochondrial NADPH through the formyl-tetrahydrofolate dehydrogenase (ALDH1L2) and releasing free folate. Studies have shown that ALDH1L2 contributes to mitochondrial REDOX homeostasis, which in turn contributes to melanoma metastasis [17]. In addition, MTHFD2 is up-regulated in many human tumors, and studies have confirmed its importance in cancer cell survival [18].

2.3 Lipid metabolism

Unlike other energy sources, abnormalities in lipid metabolism may be unique to tumor cells and have been poorly studied at the molecular level. Some cancer cells have increased fatty acid β oxidation, but most cancer cells are more dependent on lipid synthesis for energy utilization. Atp-citrate lyase (ACLY) can transform citric acid in mitochondria into acetyl-CoA in cytoplasm, which is used for lipid generation, inhibits ACLY, and attenuates tumorigenia in animal models [19], and has become a

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potential target for cancer prevention and treatment. Some lymphomas and leukemias mainly rely on ATP produced by fatty acid β oxidation [20], but the specific mechanism of fatty acid β oxidation in cancer cells remains unclear.

3. Infiltration and metastasis ability of mitochondria and tumor cell tissue

Mitochondria is an organelle with highly dynamic structure. The main difference between malignant and benign tumors lies in the tissue invasion and metastasis ability of tumor cells. Studies have shown that many tumors show morphological and distribution changes of mitochondria, and these changes are related to the invasion and migration of tumor cells. Tumor tissues have high energy metabolism and high demand. Mitochondria, as the main energy supply organelles, tend to concentrate their supply to places with high energy consumption in cells. Mitochondrial fusion and division are the two main modes of change, and they are strictly regulated by mitochondrial fission dynin-associated protein (Drp1) and mitochondrial fusion protein 1 (Mfn1) [21]. Studies have shown that there is an imbalance between mitochondrial fission and fusion activities in cancer, with increased fission activity and decreased fusion activity, and fragmentation of mitochondrial network structure. Overexpression of Mfn2 or down-regulation of Drp1 can restore the mitochondrial network structure and affect the growth of cancer cells, indicating the role of changes in mitochondrial network structure in tumogenesis [22]. In addition, the invasion and migration of tumor cells are closely related to the formation of pseudopodia, and the change of microfilaments and microtubules required for the formation of pseudopodia requires a large amount of ATP. Studies have proved that Drp1 expression is up-regulated and Mfn1 expression is down-regulated in human infiltrating breast cancer cells, so changing the expression of Drp1 and Mfn1 will affect the formation of cell pseudopodia, and thus affect the invasion and migration of cells [23, 24].

4. Cell death

Tumor formation is a favorable adaptation to an unfavorable environment for tumor cells. Tumor cells can evade immune attack by changing the way they use energy. Tumor cell metabolism tends to favor anaerobic glycolysis over the usual oxidative phosphorylation. By changing the metabolic pattern, tumor cells will change the immune function and promote immune escape. Studies have found that blocking the mitochondrial activity of tumor cells can reduce the major compatibility complex i molecule on the surface of tumor cells, which mainly helps tumor cells to resist the adaptive immune response sensitivity of tumor [25]. At the same time, after receiving the apoptosis signal, mitochondria begin to integrate and process, further magnify the apoptosis signal by releasing some pro-apoptotic substances, and finally participate in the apoptosis of cells. Apoptosis-related proteins in mitochondria determine the fate of a cell. Under normal conditions, anti-apoptotic family members such as Bcl-2 and Bcl-XL bind and inhibit Bax/Bak, while tumor cells can evade apoptosis by down-regulating pro-apoptotic genes or up-regulating anti-apoptotic genes [26]. The balance of pro-apoptotic and anti-apoptotic proteins affects the sensitivity of cancer cells to apoptotic stimuli.

As the most important tumor suppressor in cells, p53 can play a role in transcriptional regulation of cell cycle and apoptotic genes. P53 deletion or mutation is found in 50% of human tumor cells. P53 controls cell glycolysis by initiating mitochondrial electron transport chains and transcription of related genes. Mutations in P53 allow glucose to be used but not to produce energy. But recent studies have shown that p53 can help tumor cells adapt to adverse environments by increasing mitochondrial fatty acid β oxidation and respiration. P53 normally interacts with members of the Bcl-2 family to promote apoptosis, but tumor cell-derived p53 mutations no longer interact with the Bcl-2 family and do not increase permeability of mitochondrial outer membrane. Sirtuins 3 (SirT3) is located in mitochondria and is a multifunctional protein deacylase that can deacetylate a variety of substrates. SirT3 deficient mice are more prone to cancer, cardiovascular disease, neurodegenerative disease and metabolic syndrome, etc. [27]. P53 can be deacetylated by protein complexes containing histone deacetylase (HDAC1). Similarly, the presence of SirT3 may deacetylate p53 [28]. Therefore, although p53 is a tumor suppressor, its mutation can promote mitochondrial function to help tumor cells survive.

5. The mtDNA mutations

Mitochondrial DNA (mtDNA) is the only extranuclear DNA in the cells of higher animals. The role of mitochondrial DNA mutations in the occurrence and development of tumors has also attracted

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increasing attention. With the in-depth study of mitochondria and mtDNA, we find that the changes of mitochondrial structure and function and mtDNA mutations are not only related to the occurrence of many diseases, but also play a certain role in the process of tumor. Many benign epithelial tumors are characterized by accumulation of mitochondrial defects caused by pathogenic mutations in mtDNA [29]. Due to the existence of oxidative phosphorylation, mitochondria is more likely to produce hydrogen peroxide and oxygen free radicals and other substances. However, mitochondria itself cannot remove these oxides through the synthesis of glutathione, and then these oxides will damage mtDNA and eventually lead to mtDNA mutations. MtDNA mutations will weaken the normal respiratory function of mitochondria and release more reactive oxygen species, resulting in damage to the nuclear genome, inhibition of cell differentiation and the generation of tumors [30]. MtDNA lacks an effective damage repair system, but nuclear genome can, so mtDNA is relatively more vulnerable to attack by carcinogens and is an important target of carcinogens affecting the body [31]. Clinical studies have shown that mtDNA mutations of varying degrees are found in tumor tissues of patients with gastrointestinal cancer, breast cancer, ovarian cancer, bladder cancer, head and neck cancer, lung cancer and so on.

Different from the autonomous replication of nuclear genomes, the replication, transcription and translation of mtDNA are semi-autonomous. The main proteins involved in mtDNA transcription include mitochondrial RNA polymerase, mitochondrial transcription factor A (mtTFA) and mitochondrial transcription factor B2 (TFB2M). MtTFA is a key activator related to mitochondrial transcription, which can help mitochondrial RNA polymerase recognize and bind sequence elements in its promoter region by changing the light chain promoter structure in the d-ring region of mitochondria, and ultimately promote mtDNA transcription [32]. Abnormal expression of mtTFA is closely related to the occurrence and development of various tumors [33]. Studies on the expression of mtTFA in various tumors show that it can reflect the biological behavior of various tumor cells and is a potential tumor biomarker. At the same time, clinical data showed that mtTFA was significantly correlated with the prognosis of tumor patients, and down-regulation of its expression was correlated with the proliferation inhibition of tumor cells. Therefore, mtTFA can also be used as a potential target for disease treatment and human function improvement.

In addition, mtDNA plays an important role in regulating respiratory chain together with nuclear genes, and its mutation may be one of the endogenous factors inducing nuclear gene mutation, which may promote the occurrence of tumors [34].

6. Oxidative stress

Biological metabolic reactions produce ROS and hydrogen peroxide, which are formed by superoxide and hydroxyl radicals. Mitochondria are major intracellular ROS contributors, but they contain a variety of antioxidants that neutralize ROS damage, including superoxide dismutase (SOD2), glutathione, thioredoxin, and peroxydoxin. Previous studies found significant high levels of ROS in cancer cells and proposed the hypothesis that inhibition of ROS can treat cancer, but current studies found that up-regulation of antioxidant expression can inhibit ROS-mediated cytotoxicity, and ROS at this time can stimulate the conduction of signal pathways and enhance the survival of tumor cells [35].

High levels of ROS contribute to the oxidation of macromolecules such as lipids, proteins and DNA, contributing to genomic instability. Moderately elevated ROS has been observed in many tumors to regulate cellular signaling through oxidation of cysteine. Hydrogen peroxide inactivates tumor suppressor gene PTEN by oxidizing active sites of cysteine residues [36]. ROS can also inactivate tyrosine phosphatase by oxidizing cysteine residues, which mediate carcinogenic signaling pathways that affect the migration and metastasis of cancer cells in multiple tumor types. Increased ROS levels in tumors up-regulate many protective antioxidant pathways, for example, oncogenic K-Ras, B-Raf and C-Myc effectively inhibit ROS by regulating NRF-2 (a transcriptional regulator of antioxidant response), thereby promoting tumor genesis [37]. Tumor cells can maintain ROS levels in a range that can stimulate proliferation without causing cytotoxicity.

Upregulation of antioxidants can also be a breakthrough in the treatment of tumors. In vivo and in vitro experiments in breast cancer models provide the possibility of using a combination of glutathione and thioredoxin inhibitors. Antioxidants can be used to prevent the formation or progression of precancerous lesions, or to increase ROS in tumor cells to toxic levels [38]. In addition, therapies that target REDOX regulation in mitochondrial metabolism have proven to be a successful anticancer strategy.

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7. Autophagy and mitochondrial autophagy

Autophagy is a major pathway in which cells participate in lysosomal degradation of proteins and organelles. Mitochondrial autophagy degrades mitochondria through autophagy. Studies have shown that mitochondrial autophagy has selective specificity and is precisely regulated by various factors in mitochondria, which is an important regulatory mechanism for the body to eliminate aging or damaged mitochondria in vivo and maintain mitochondrial homeostasis. Abnormal mitochondrial autophagy is closely related to neurodegenerative diseases such as Parkinson's disease. Mitochondrial autophagy can not only eliminate those dysfunctional mitochondria, but also reduce the total number of mitochondria required by environmental stress (hypoxia or malnutrition).

Mutations in PARK2 (Parkin) and PARK6 (PINK1) gene products in human Parkinson's disease promote mitochondrial autophagy in a synergistic way, suggesting the emergence of dysfunctional mitochondria in Parkinson's disease [39]. Deletion of the PARK2 (Parkin) gene is found in ovarian, breast, bladder, lung and other cancers. In mouse model experiments, we found that parkin deletion mice are susceptible to spontaneous liver tumors, which may be related to parkin's role in lipid metabolism. Parkin expression can increase oxidative metabolism and limit the Warburg effect downstream of tumor suppressor p53, so as to ensure mitochondrial integrity [40]. It has also been documented that Parkin regulates the expression of cyclin D1, cyclin E, and CDK4 in cancer, suggesting that Parkin not only plays a role in mitochondrial autophagy, but also plays a role in tumor suppression by inhibiting cell cycle.

Hypoxia occurs in solid tumor tissues, and mitochondrial autophagy has become a key adaptive response of cells to hypoxia, because cells reduce the number of mitochondria, which not only limits the production of ROS, but also maximizes the utilization of available oxygen. Two key substances involved in promoting mitochondrial autophagy under hypoxia are BNIP3 and NIX, both of which are downstream target genes of HIF-1 [41]. Both BNIP3 and NIX are regulated by p53. Increased expression of BNIP3 and NIX was observed in all kinds of non-apoptotic cell death induced by stress. Increased expression of BNIP3 and NIX was found in ductal carcinoma in situ of human breast cancer, and loss of BNIP3 protein and mRNA expression was found in invasive ductal carcinoma of breast, suggesting that they are associated with proliferation and metastasis of tumor cells. Deletion of BNIP3 expression has also been reported in other cancers, including blood and lung cancer, stomach cancer, pancreatic cancer and liver cancer. Especially in pancreatic cancer, the inactivation of BNIP3 is closely associated with chemotherapy resistance and poor prognosis.

Although a large number of literatures indicate that the loss of mitochondrial autophagy can promote the early growth of tumors [42], autophagy plays a dual role in advanced and invasive diseases, that is, inhibiting the early stage and promoting the late stage [41]. Based on the inhibition of mitochondrial autophagy caused by the deletion or inactivation of Parkin and BNIP3 genes and the promotion of tumor formation, especially for the induction of Warburg effect, targeted mitochondrial autophagy has been proposed as a treatment method for tumors. Chemical inhibition of mitochondrial autophagy is also an effective treatment for advanced tumors that have been converted to glycolysis but still rely on other metabolic functions of mitochondria. However, compared with normal cells, tumor cells produce more ROS, and inhibition of mitochondrial autophagy will aggravate the increase of ROS. Therefore, although this method can effectively kill tumor cells, it is not sure about the damage to normal cells. So this treatment needs to be studied in more detail.

8. Conclusion

Mitochondria are complex organelles that affect tumorigenesis, growth, survival and metastasis. Many aspects of mitochondrial biology can affect tumorigenesis. The interaction between various mitochondrial physiological functions makes mitochondria regulate the stability of cell life activities and highlights the pluripotency function of mitochondria in cancer. In addition, similar to the discovery of oncogenic mutations in growth factor signaling pathways, mutations in mitochondrial metabolic enzymes are new discoveries in cancer treatment research [41]. Mitochondria give tumor cells flexibility in energy use, allowing them to survive harsh conditions. The study of mitochondrial function helps us to better understand the development of cancer cells. However, the biological energy of mitochondria varies from cancer cell to cancer cell, partly depending on the degree of differentiation of the cancer cell. Therefore, in order to effectively treat cancer, we must pay more attention to the study of mitochondrial biology.

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