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The Role of Mitochondria in The Development and Progression of Cancer

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Abstract

Mitochondria are the extra-nuclear source of DNA in cells and play an important role in cell death susceptibility, oxidative stress regulation, metabolism, and signaling in normal cells. Because of this, its dysfunction can contribute to the progression of cancer and metastasis. Also, mtDNA mutations have been reported in many cancers, followed by altered mitochondrial activity and cellular signaling . This increase in mtDNA mutation is due to the proximity of the genome to the OXPHOS system which are thought to be more in extent than mutation nuclear. These mutations do not inactivate energy metabolism but change its state. Therefore, it is not surprising that the function of mitochondria is vital for cancer cells, in addition to understanding the mechanisms of mitochondrial function in the process of tumor formation and cancer progression is essential for cancer treatments.

INTRODUCTION

Mitochondria is tubular organelles and 0.5 to 3 µm long (1). They have outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM) which surround intermembrane space (IMS). Mitochondria matrix is in the inner area of organelle. OMM is considered a surface for exchanging and signaling (2). IMM has low permeability and is a place where electron transport chain (ETC) takes place and ATP and superoxide are produced (3, 4). In addition, mitochondria have roles in many important cell activities such as cell cycle control, apoptosis control and cell proliferation(5). Matrix is an area for mitochondrial DNA (mtDNA) replication, transcription , macromolecules synthesis and the reactions of tricarboxylic acid (TCA) cycle (6). The phrase "mitochondrial medicine" was coined in 1962 by Rolf Luft in his clinical report related to increased non-thyroid metabolism (7). A large number of specific syndromes are concerned with clinical mutations of mitochondrial diseases, that is why mtDNA is described as pathogenic Pandora's box (8). Due to mitochondria's important roles as in apoptosis, it is not wondering that mitochondrial disorders have impacts on diseases such as cancer, and mitochondria have been considered in relation to neoplasia (9-11). In early 1920, Warburg was a pioneer in studies referred to mitochondrial respiration. He suggested a mechanism for explaining mitochondria contribution in the carcinogenic process (12). Warburg reported that tumors manufacture extra lactate in the hypoxia. This findings became known as "Warburg effect". He explained it as mitochondrial dysfunction(13). In the field of "oncologic mitochondria" polymorphisms and specific mutations which are important for diagnosis and prognosis are studied and analyzed (14). In this review, we examine the oncological mechanisms of mitochondria involved in the development and progression of carcinogenesis.

mtDNA mutations

Mitochondria are the extra-nuclear source of DNA in cells (15). mtDNA is a double-stranded circular molecule which has 16569 base pair and contains 37 genes for expression 22 tRNAs, 2 rRNAs (12s and 16s) and 13 crucial polypeptides for OXPHOS system(16). mtDNA mutations are thought to be caused by the nearness of the genome to the OXPHOS system, which is located in the IMM of the mitochondria. Therefore, it makes mitochondria vulnerable to leakage of reactive oxygen species (ROS) while OXPHOS function. This increase in mtDNA sensitivity leading to several mutations which are thought to be more in extent than nuclear DNA(17) The mtDNA has unique

characteristic that distinguish it from the nuclear genome. It is inherited natively and there are several hundred in one cell. In addition to, based on tissue's requirement to energy, The count of copies varies in several cell types (18). Displacement loop (D-loop) is the sole majer non-coding area in mtDNA. D-loop is shaped by the relocation of two genomic strands and the involvement of a third strand of DNA and is a 1.1 kb area which contains significant control components for DNA transcription replication in Mitochondria (19). Also, many wrong mutations identified in the neoplasm of primary human areoften found in non-coding D-loop region. These mutations lead some shifting in the framework of mtDNA (20). For instance, mtDNA mutations in D-loop region is a commonplace in liver cancer in a way that in one study 68% of patients were diagnosed with this mutation(21). Similarly, some prostate cancers are associated with mutations in the D-loop region of Complex I (22). Pathogenic mutations in mtDNA are mainly associated with changes in electron transport chain (ETC) subunits (23). For example, some neural cancers have mutation in succinate dehydrogenase (SDH, complex II) (24). Mutations in different coding and control regions of mtDNA have reported in cancer cells of intestine (20), prostate cancer (22, 25) and other types of solid tumors (25). Oncocytoma is a rare and benign tumor in most regions of epithelium associated with defective inspiration of mitochondria caused by pathogenic mutations in mitochondria genome and the accumulation of defective mitochondria (26). Furthermore, mtDNA has a significant role in cell sensitivity to cancer treatment's agents (27). For instance, reduction or deletion of mtDNA is effective in carcinogenesis or progression of gastric carcinoma (28). In addition, the results of a study indicate that patients with high level of mtDNA are at higher risk for colon cancer(29). Similarly, the results of another study indicated that a high level of frequency occur in the structure of mtDNA during colon cancer development (30). For this reason, looking for mutations in mtDNA structure would be an early diagnosis for cancer. Additionally, applying mutations or polymorphism patterns in mitochondrial genes of tRNA such as A12308G, a polymorphism mutation in V-loop $tRNA^{Leu(CUN)}$, is developing rapidly as a biologic marker in a variety of cancers , because tRNA genes accomplish a variety of roles, including processing and translation considered important constituent of mitochondrial protein synthesis (31). Mutations in mitochondrial genes which are encoded by nuclear DNA is also associated with cancer (32). mutations of nDNA genes involved in mitochondria metabolism inclusive fumarate hydratase (FH), Isocitrate dehydrogenase (IDH1) , (IDH2) and succinate dehydrogenase (SDH), increase succinate, fumarate, or R(-)-2-hydroxyglutarate level. These metabolism changes can inhibit different dioxygenases relied on α-ketoglutarate. Also, they can activate stress reaction pathway of NFE2-related factor 2 (NRF2) (33). All of these effects can lead to tumors.

Mitochondrial ROS (mtROS)

The mitochondrial genome is prone to mutations due to the high level of production of reactive oxygen species (ROS) in this organelle, along with the low level of DNA repair (34-37) and it can be the most significant stimulus to develop cancer and its progression to malignancy(38). ROS is mainly generated by mitochondria. Superoxide is released as a byproduct in oxidative respiration (39). In general, ROS is in the form of superoxide (°- O_2), hydroxyl radical (OH) and hydrogen peroxide (H_2O_2) (3). Two sites in respiration chain included complex I and complex III are suggested as the main source of mitochondria ROS (mtROS) (40-42). ROS can be generated in The tricarboxylic acid cycle or ETC pathway. However, it is mainly generated in ETC by electron leakage at connecting sites of ubiquinone in complex I (IQ site) and complex III (IIIQ site) process electron transporting (43). Superoxide production is completely reduced or partially reduced primarily by the donation of an electron from electron carriers(3). Due to its high reactivity, °- O_2 is immediately converted to H_2O_2 under the catalysis of mitochondrial SODs. There are SOD1 in intermembrane space and cytosol which inactivate superoxide generated by complex III in ETC. While SOD2s are in mitochondrial matrix and they inactivate superoxide generated by complex I and complex III (3). In addition to connective sites for ubiquinone in complex I and complex III of ETC, other sites which generate ROS are marked: Flavin in complex I (IF site), electron which transfer flavoprotein Q oxidoreductase (ETFQOR) in FAO, pyruvate dehydrogenase, glycerol-3-phosphate dehydrogenase and 2-Oxoglutarate dehydrogenase (44). H_2O_2, which is semi-resistant, can exit mitochondria and release to cytosol and nucleus where it can act (45). H_2O_2 reaction with phosphatases including protein kinase phosphatase activated by mitogen (MKP) can inhibit their dephosphorylation. For instance, it activates cJun N-terminal kinase (JNK) (46). Hypoxia increases production of ROS in complex III which leads to the accumulation of HIF-1α protein responsible for hypoxic response. This response dies out in cells without mitochondrial DNA (47). Mutated mtDNA by ROS leads to invasion and metastasis in lung and breast cancer cells (48, 49). The results of a study indicate that ROS can increase ΔmtDNA4977 mutation in gut cancer (50). Also, it has been suggested that the increase of ROS generation as an essential factor in tumorigenesis is involved in p16ink4a and p53 inactivation (51). Additionally, same

as ROS importance in tumorigenesis. Mutations in the promoter of mitochondrial manganese superoxide dismutase gene have been observed in a number of tumors such as prostate cancer (25, 52). In a study, it has been showed that critical mutations of COI in mtDNA related to prostate cancer, increase ROS generation and their in vivo development (25). Also, ROS generation in cancer cells inhibition caveolin 1 in Stromal fibroblasts and it in intensifications mitophagy, reduce mitochondrial function and increases lactate production in these fibroblasts. Secreted lactate from stromal cell, amplifies oxidative metabolism of cancer cells which leads to tumor development, which is said "Reverse Warburg effect" (33).

Mitochondrial Oncometabolites

Dominant mutations in mitochondrial enzymes led to the identification of mitochondrial signaling molecules named oncometabolites. Among metabolic pathways in mitochondria, tricarboxylic acid (TCA) cycle is a focal point in oncology. Mutations in the enzymes of TCA cycle are found in human cancers with the nucleus code of Isocitrate dehydrogenase 2 (IDH), succinate dehydrogenase x (SDH) (SDHA-SDHD and SDHAF2) and fumarate hydratase (FH) (53). Isocitrate dehydrogenase (IDH) catalyzes reverse transformation of Isocitrate to 2-Oxoglutarate (OG). In eukaryotes, IDH3 is isoform dependent on Nicotinamide adenine dinucleotide (NADH) IDH1 and IDH2 are isoforms dependent on Nicotinamide adenine dinucleotide phosphate (NADPH). Cytoplasmic NADPH-dependent isoforms (IDH1) and mitochondrial NADPH-dependent isoforms (IDH2) have been reported in different tumors such as colon cancer (54), prostate cancer (55), glioblastoma (56), acute myeloid leukemia (57) glioma (58), acute lymphoblastic leukemia B (55), cholangiocarcinoma in liver (59) and osteosarcoma (60). Oncogenic mutations provide neomorphic activity for IDHs which convert OG to R-enantiomer 2-hydroxyglutarate (R-2HG) instead of isocitrate to OG conversion. R-2HG accumulates in cancer cells up to millimolar level (61, 62). Cells incubation with R-2HG blocks the differentiation of blood-forming cells led to blood cancer (63). This weak metabolism is at the moment considered as a main agent in the carcinogenic activity of mutated IDHs. Succinate dehydrogenase (SDH) is a complex of enzymes, which is bond to inner membrane of mitochondria and converts succinate to fumarate. It is considered the only known enzyme in respiration chain which is encoded completely by nDNA and has no proton pumping action. Inherited scattered mutations in SDH subunits are associated with cancers such as hereditary paraganglioma, pheochromocytoma (64), kidneys cancer (65), gastrointestinal stromal tumor (66) and breast cancer (67). Most of the oncogenic activities of SDH mutations have been attributed to succinate metabolism which accumulate in cells without SDH. Carcinogenic role of succinate is primarily associated with PHDs inhibition and HIF stabilization (68). Also, it has recently been showed that succinate is an epigenetic hacker (69) which leads epigenetic changes overlapped with observations of mutated IDH in cancers (70). Fumarate hydratase (FH) converts fumarate to malat. Germinal mutations in FH discovered in renal cell cancer and hereditary leiomyomatosis (71). Also, it was found that FH in Glioblastoma (72), non-Myc-amplified neuroblastoma has been removed (73) and sporadic clear cell carcinoma (74). So that, partially of its tumorigenic action has been attributed to atypical aggregation of fumarate in cancer cells with deficient amount of FH that reaches up to millimolar level (75). There are some similarities between fumarate and 2HG. That is why fumarate can inhibit different OG-dependent enzymes including PHDs (76). Furthermore, fumarate is an α,β-unsaturated electrophilic metabolite which can covalently bind to cysteine protein remainders by succination (77).

Carcinogenic signaling pathways and regulation of metabolism

Regulation of energy metabolism can be found in triple transcription factors: p53, HIF-1 and c-MYC. Oncogenic changes include an accidental system of deletion and duplication mutations in genes. Many of the carcinogenic genes and those who inhibit tumors are along with signaling pathways that regulate p53, HIF-1 and c-MYC (78). The main activator is mitochondria biogenesis is c-MYC in cancers. It is a transcription factor which regulates cell cycle, cell growth, metabolism and apoptosis widely. More than 400 mitochondrial genes targeted by c-MYC have been discovered. Primary studies indicated that Increase and loss of c-MYC increase and decrease mitochondrial mass, respectively (79). HIF-1 and c-MYC are known as the two major factors in glycolysis stimulation by direct or indirect activation of glycolytic genes. These two transcription factors coordinate the expression of glycolytic key enzymes such as LDHA, TPI1, PFK1 and HK2 in other tumors (80-82). In contrast, p53 suppresses glucose absorption by inhibiting the transcription of glucose transporters such as Glut1 and Glut4 (83, 84) directly and by suppressing Glut3 expression (84). Glut3 is a target gene for NF-κB and p53 blocks NF-κB activating. As a result, it reduces glut3 transcription and expression considerably (84). Also, p53 induces TP53-induced glycolysis and apoptosis regulator (TIGAR) expression to decrease glycolytic speed of cancer. TIGAR can lower ROS levels and reduce sensitivity to p53 and other apoptotic signals related to ROS and may be an important

component in mediating the suppressive effects of p53 tumor (85). Recent studies indicate that the increase in oncogenes function or inhibitor of tumor suppressed genes regulate high levels of glycolytic in tumor cell (86). Because of this reason, signaling molecules associated with cell proliferation such as PI3 and KRAS are deliberate vital regulators in metabolic pathways (87). In addition, it was reported that Akt oncogene which often increased in cancer cells has a straight stimulated action on glucose metabolism in cancer cells. Akt signaling is regulated by the activation of growth factor receptor. Pathway of Akt signal transfer involves the activation of oncoproteins and the inhibitor of tumor suppressors (88). PI3K/Akt signal which is in the downstream of tyrosine kinase receptor (RTK), increases glucose absorption through GLUT1 carrier and as a result increases glycolysis. Branches of glycolytic metabolism contribute to the synthesis of nucleotides and amino acids (89). The activation of Akt signaling pathway is a repetitive molecular shift in destructive tumors. Thereupon, targeting Akt signaling pathway is a sensible approach to cancer treatment (90). One of the main pathways in substances absorption into cells is mammalian target of the rapamycin (mTOR) which is located on the downstream of PI3K/Akt signaling. mTORC1 combines nutrients and intracellular energy signals with mediated upstream signals of PI3K/Akt growth factor receptor through a network of downstream signaling pathways. So it regulates a complex of anabolic and catabolic reactions(91). In cancer, the overactivity of PI3K/Akt, along with reduced regulation by AMP-kinase (AMPK), leads to mTOR overactivity (92) and mTOR signaling partly induces the biogenesis of mitochondria through proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) (93) which is a central regulator in mitochondrial biogenesis through interaction with several transcription factors. PGC-1a levels often show tumor correlation to mitochondrial mass. High level of GPG-1a expression leads to mitochondrial inspiration (94). Furthermore, PGC-1α in renal carcinoma cells decreases by hypoxia inducible factor-1 alpha (HIF-1a), which is activated in hypoxia state. So it makes some changes in glycolytic metabolism in hypoxia state (95). Also, mitochondrial PGC-1a-dependent biogenesis supports the growth of cancer cells which is a key step to metastasis (96). Cancer cells can adapt their mitochondrial function based on the special stress in environment. For instance, overregulation of c-Myc and the expression of glycolytic gene lead to resistance to metformin, complex I inhibitor, in cancer cells of pancreas. c-Myc uses mitochondrial respiration actively due to PGC-1a expression (97). Thus, control and signaling pathways of metabolism is a critical point in cancer treatments.

Escape from apoptosis

The hallmark of cancers is their ability to escape from apoptosis, a process which has a close correlation with mitochondria. The member of Bcl-2 family such as Bak and Bax enter OMM and they become to some oligomerizations to produce mediate mitochondrial outer membrane permeabilization (MOMP). As a result, by the formation of pores and the release of cytochrome c from the mitochondria into the cytosol, caspases are activated and apoptosis happens (98) Cancer cells often block apoptosis by modulating of anti-apoptosis proteins such as BCL-2 which prevents MOMP production (99). Many of the studies have indicated that overregulation of BCL-2 anti-apoptosis proteins is a common property among cancers. Modulating mechanisms are different but they include enhancing of copy numbers, transcription regulation (by the use of oncogenic signaling) or, erroneous regulation of microRNAs which suppress the expression of BCL-2 anti-apoptosis protein (100, 101) For instance, in a study it has been showed that cancer cells have some enhancers in the vicinity of MCL1 and BCL2L1 anti-apoptosis genes that require the expression of these genes to survive (100). In addition, cancer cells inhibit caspase function following the MOMP (102). These cells inhibit caspase function through different ways. They turn off APAF-1 by epigenetic and phosphorylation so they reduce apoptosis reaction. Besides, cytochrome c can be targeted after MOMP by proteasome and be degraded. As a result the The activity of proteins involved in apoptosis remains ineffective (103). Caspase function can be inhibited directly by XIAP and indirectly by c-IAP1 or c-IAP2 through their ability to bind and neutralize XIAP SMAC and Omi inhibitors (104).

Mechanisms of Metastasis by Mitochondria

A mechanism named mitochondrial transmission supports tumor metastasis and invasion widely. Mitochondrial transmission occurs in cells which are not able to have aerobic respiration due to the defect in their mtDNA (105). mtDNA transmission from host cell to the tumor cell increases tumor ability because cancer cells reduce respiration, and horizontal transmission in these cases increases the invasion of cancer cells. It also protects cancer cells from chemotherapy (106). Additionally, in vivo transmission of mitochondria leads to recurrence of the disease. It generally increases the aptitude of tumor cells to overcome adverse condition by altering metabolism (107). So, in a study it has been reported that mitochondrial transmission in tumor models of mice is contributed to essential consequences in functions for tumor growth and metastasis (108). The studies indicate that syntaphilin (SNPH) is involved in mitochondria attachment to microtubules and it is

the main regulator in mitochondrial transmission and tumor invasion (109). Hypoxia is also controls the transmission of mitochondria. Tumor cells reduce the level of SNPH protein and mRNA which increase invasion in glioblastoma cells. Furthermore, tumors stabilized by HIF-a reduce SNPH which shows the critical role of SNPH in metastasis (109). Another involved factor in metastasis is mROS. mROS caused by oxygen deficient activates HIF-1 which facilitates metastasis by increasing glycolyticenzymes expression due to the altered metabolism of OXPHOS. In contrast, HIF-1 reduces mROS generation and facilitates tumor growth and metastatic cells residue which indicates the functional role of mROS in different cancers (110). Therefore, dispersion of metastasis is difficult by ROS. High levels of ROS inhibit metastasis in melanoma while ROS increases metastasis in other cancers (111).

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