Minireview

Role of the mitochondrial stress response in human cancer progression

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Impact statement

Dysregulated mitochondria often occurred in cancers. Mitochondrial dysfunction might contribute to cancer progression. We reviewed several mitochondrial stresses in cancers. Mitochondrial stress responses might contribute to cancer progression. Several mitochondrion-derived molecules (ROS, Ca^{2+}, oncometabolites, exported mtDNA, mitochondrial double-stranded RNA, humanin, and MOTS-c), integrated stress response, and mitochondrial unfolded protein response act as retrograde signaling pathways and might be critical in the development and progression of cancer. Targeting these mitochondrial stress responses may be an important strategy for cancer treatment.

Abstract

Mitochondria are important organelles that are responsible for cellular energy metabolism, cellular redox/calcium homeostasis, and cell death regulation in mammalian cells. Mitochondrial dysfunction is involved in various diseases, such as neurodegenerative diseases, cardiovascular diseases, immune disorders, and cancer. Defective mitochondria and metabolism remodeling are common characteristics in cancer cells. Several factors, such as mitochondrial DNA copy number changes, mitochondrial DNA mutations, mitochondrial enzyme defects, and mitochondrial dynamic changes, may contribute to mitochondrial dysfunction in cancer cells. Some lines of evidence have shown that mitochondrial dysfunction may promote cancer progression. Here, several mitochondrial stress responses, including the mitochondrial unfolded protein response and the integrated stress response, and several mitochondrion-derived molecules (reactive oxygen species, calcium, oncometabolites, and others) are reviewed; these pathways and molecules are considered to act as retrograde signaling regulators in the development and progression of cancer. Targeting these components of the mitochondrial stress response may be an important strategy for cancer treatment.

Keywords: Mitochondria, cancer progression, retrograde signaling, mitochondrial stress response, integrated stress response, unfolded protein response

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Introduction

The earliest report of the existence of mitochondria traces back to the 1840s.[1] In the 1890s, the term mitochondria was introduced by combining Greek terms mitos (thread) and chondros (granule), according to their special morphology during spermatogenesis.[1] Mitochondria are the major energy-producing organelles in eukaryotic cells, and they are responsible for converting nutrients into usable energy sources, such as adenosine triphosphate (ATP), through oxidative phosphorylation (OXPHOS) in conjunction with the citric acid cycle.[2] In addition to glucose metabolism, mitochondria carry out fatty acid β-oxidation and amino acid metabolism.[3,4] Mitochondria also play critical roles in numerous physiological processes such as programmed cell death, innate immunity, autophagy, redox homeostasis, and calcium homeostasis.[5–7] In addition, mitochondria are essential regulators of stem cell activation and fate decisions.[8] Reactive oxygen species (ROS) are byproducts of OXPHOS and are linked to several diseases, such as aging, neurodegenerative disease, diabetes, and cancer.[9,10] Mitochondria have their own genome mitochondrial DNA

(mtDNA), that is located in the mitochondrial matrix. The number of mtDNA copies in each mitochondrion usually varies.[11] Human mtDNA is a double-stranded, circular DNA molecule, approximately 16.6 kb in size, that contains the genes of 2 rRNAs, 22 tRNAs, and 13 subunits of the respiratory enzyme complex for the OXPHOS system.[11] The biogenesis of mitochondria requires tight coordination between the genomes of the mitochondria and nucleus.[12]

Deregulation of cellular energetics is proposed as one of cancer hallmarks.[13] In the 1920s, Otto Warburg[14] proposed that cancer cells utilize glycolysis instead of mitochondrial OXPHOS for glucose metabolism even in aerobic condition. Normal cells can metabolize glucose through mitochondria under oxygen abundant circumstance, but in the absence of oxygen, glucose will be converted into lactate by glycolysis. Although cancer microenvironment is nutrient and oxygen limited, cancer cells highly utilize glucose in the presence of oxygen and elevate lactate production. This was thus suggested by Dr. Warburg that there were defects in OXPHOS or mitochondrial respiration in cancer, and which forced the cells to revert to glycolysis.[14] This metabolic characteristic provides the base for clinical use of ^{18}F-fluorodeoxyglucose positron emission tomography (PET) in cancer diagnosis. The Warburg effect has led to identification of the cause factor for mitochondrial dysfunction in cancer, though recent studies showed that cancer cells have intact mitochondrial metabolism.[15,16]

Tight coordination and communication between mitochondrial and nuclear genomes are essential for the maintenance of mitochondrial function. The nuclear genome can regulate mitochondrial activity depending on cellular needs for proliferation through anterograde regulation. Conversely, mitochondria can further regulate the expression of nuclear genes to modify cellular function and cell metabolism remodeling via retrograde signaling. The mitochondria-to-nucleus signaling pathway was first identified in yeast. The Rtg family proteins are the major regulators of retrograde signaling[17–19] and are essential for maintaining yeast survival under OXPHOS-deficient circumstances.[18,20] However, the mammalian orthologs of Rtg proteins have not yet been identified.[21] In mammalian cells, mitochondrial retrograde signaling was first proposed in skeletal myoblast cells and later confirmed in human lung cancer cells.[22,23] Several types of mitochondrial retrograde signaling have been identified and largely investigated in cancer cells.[24,25] Mitochondrial dysfunction can be caused by various mitochondrial stresses, such as mtDNA mutations, mitochondrial enzyme defects, mitochondrial dynamic changes, and mitochondrial unfolded protein accumulation. The mitochondrial stress responses not only reprogram cellular energetic metabolism but also induce signaling for cancer progression by releasing ROS, Ca^{2+}, some metabolites/proteins, or mitochondrion-derived molecules from mitochondria. In this minireview, we discuss what factors may contribute to mitochondrial dysfunction in cancers, how mitochondrial dysfunction promotes cancer progression, and the role of the mitochondrial stress response in cancer progression.

The factors contribute to mitochondrial dysfunction in cancers

Defective mitochondria and increased aerobic glycolysis are frequently observed in cancer cells compared to normal cells. The mechanistic understanding of what factors contribute to mitochondrial dysfunction and how they further regulate cell growth and carcinogenesis is expanding beyond the Warburg effect as an area of research that is underexplored in terms of its significance for clinical application in cancer prevention and treatment.

MtDNA copy number changes and mutations in cancers

In human cancers, several mtDNA alterations have been identified, such as mtDNA copy number changes, point mutations, insertions, and large-scale deletions.[26] MtDNA mutations may also provide a powerful molecular diagnostic marker for noninvasive detection of cancer because mutated mtDNA can be detected in number of cancers.[27]

MtDNA copy number alterations can change mitochondrial function.[28] Great variations in mtDNA copy number are detected across various cancers. An increase or decrease in mtDNA copy number may be tissue specific in different types of cancers. In glioma, endometrial adenocarcinoma, lymphoma, esophageal squamous cell carcinoma, and colorectal cancer, the mtDNA copy number is increased.[29–33] On the other hand, the mtDNA copy number is decreased in most hepatocellular carcinomas (HCC, 60%), gastric cancers (55%), and breast cancers (63%).[34–38]

The majority of somatic mutations in mtDNA are located in the D-loop region (51%), followed by the protein coding region (40%), rRNA genes (5%), and tRNA genes (4%).[26,39] The D-loop is thus thought to be a "hot spot" for the mutation of mtDNA in tumors.[27] Mutations in the D-loop region may induce mitochondrial dysfunction and subsequently elevate ROS production, which may contribute to cancer initiation.[40,41] The D-loop region is responsible for the replication and expression of the mitochondrial genome. Somatic mutations in the mtDNA D-loop coincide with decreased mtDNA copy number in several human cancers.[34–36,38]

MtDNA mutations in the protein coding region have high potential to induce mitochondrial dysfunction in cancer.[39] Some of these somatic mtDNA mutations are pathogenic in patients with mitochondrial disorders.[42,43] Moreover, several somatic mtDNA mutations may result in missense, nonsense, or frame-shift mutations, which potentially lead to mitochondrial dysfunction.[42–44] These findings support that somatic mutations in the protein coding region of mtDNA can lead to mitochondria defects during tumorigenesis.

Most of the somatic mtDNA mutations are homoplasmic, indicating cancer cells harboring mutated mtDNA become dominant in tumor. The homoplasmic mtDNA mutations in cancer cells might be through selection process during cancer development.[45,46] Pathogenic mtDNA mutations give an advantage in tumor growth and overcome wild-type mtDNA in the promotion of tumors.

Large-scale deletions of mtDNA, especially the 4977-bp common deletion that result in the loss of 5 tRNA genes and 7 protein-coding genes, have been detected in various cancers.[34,35,47–52] The mtDNA 4977-bp deletion is considered a pathogenic mutation in human cells. It can lead to completely impaired energy production and subsequently induce mitochondrial dysfunction.[53] A correlation was found between the 4977-bp deletion and betel quid chewing history in oral cancer patients, which suggests that the accumulation of this deletion may play an important role during the early phase of oral carcinogenesis.[54] Moreover, NADPH quinone oxidoreductase 1 (NQO1) deficiency-mediated ROS elevation may contribute to mtDNA 4977 deletion in breast cancer patients.[55] However, lower levels of the mtDNA 4977 deletion in tumors were noted than in nontumor tissue in different kinds of cancers, such as gastric cancer and colorectal cancer.[34,56] The low accumulation of mtDNA 4977 deletion in the cancerous area might be the consequence of a dilution effect after cancer progression or a selection process that eliminates cancer cells harboring the mtDNA deletion.

In cancers, most somatic point mutations in mtDNA are homoplastic. Large-scale mtDNA deletions accumulate less readily in tumor tissue than in nontumor tissue. The mtDNA copy number decrease alone might not affect the homoplasmic/heteroplasmic level of the point mutation or the accumulation level of large-scale deletions in the mtDNA of cancer cells.[57] These results suggest that mitochondrial genome instability and reduced mtDNA copy number may be independent of each other in human cancer.

The mitochondrial genome is highly susceptible to oxidative damage and mutation because ROS are byproducts of OXPHOS and mtDNA lacks efficient DNA repair systems.[58] Mutated mtDNA-mediated mitochondrial dysfunction can increase ROS production.[59] ROS might be a causing factor for mtDNA mutation. Moreover, ROS may stimulate several signaling pathways to maintain homeostasis. Therefore, ROS play a dual role as an inducer as well as a protector via apoptosis signals against cancer depending upon the development stage of cancer.[60,61]

In the past decades, the mitochondrial alterations have been studied in detail with the advances of biotechnology. We realize that the cancer cells do not exhibit universal pattern such as mtDNA copy number alterations. This may be due to tumor heterogeneity arising from the heritable causes or the origin of tumor such as regional differences in the tumor (e.g. various structures of blood and lymphatic, different types and amounts of infiltrated normal cells, and different extracellular matrix composition).[62]

Mitochondrial enzyme defects and mitochondrial dynamic changes in cancer

Mitochondrial enzyme defects and mitochondrial dynamic changes can lead to mitochondrial dysfunction. Although mitochondria contain mtDNA, most proteins are encoded by nuclear DNA.[63] Mitochondrial stress might also be induced by defects in nuclear-encoded mitochondrial enzymes, such as citric acid cycle enzymes or other mitochondrial proteins, such as sirtuin 3 (SIRT3), which is responsible for the deacetylation of mitochondrial proteins.

Mitochondrial enzyme defects

Mutations in fumarate hydratase (FH), succinate dehydrogenase (SDH), and isocitrate dehydrogenase (IDH), which are nuclear genome-coded mitochondrial enzymes, have been found in cancers.[64–66] The FH germline mutation might contribute to increased cancer risk in renal cell carcinoma and uterine leiomyosarcoma.[67] SDH complex subunit A (SDH-A) germline mutations might be a driver of tumorigenesis in neuroblastoma.[68] Moreover, IDH mutations might promote the development of a number of malignancies, such as glioma, myeloid neoplasia, chondrosarcoma, and cholangiocarcinoma.[69,70]

SIRT3 (mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase, sirtuin-3) is responsible for protein deacetylation and regulates mitochondrial activity and energy metabolism.[71] SIRT3 regulates the redox status, stress response, and aging. SIRT3 defects are associated with different cancers, such as oral cancer, breast cancer, and HCC.[72–74] SIRT3 may act as a tumor suppressor in gastric cancer.[75] Moreover, SIRT3-mediated deregulation was found to decrease the expression of the mitochondrial DNA repair gene (8-oxoguanine DNA glycosylase, OGG1-2a) and to increase proliferation activity, which may be important factors in the development of head and neck squamous cell carcinoma.[76] These results suggest that mitochondrial enzyme defects can contribute to tumorigenesis.

Mitochondrial dynamic changes

In mammalian cells, mitochondria are highly dynamic organelles that have tightly coordinated cycles for fission and fusion, which are processes involved in "mitochondrial dynamics." Changes in mitochondrial dynamics can regulate the shape, distribution, size and function of mitochondria. Mitochondrial dynamics play an important role in many cellular homeostasis, such as cell cycle, immunity, apoptosis, and mitochondrial quality control.[77]

Mitochondrial dynamics is responsible for the altered extracellular nutrient level.[78] Moreover, cancer metabolism has its flexibility to the surrounding nutrient availability.[79] In addition, cancer cells acquire different metabolic remodeling corresponding to their malignant stages, such as rapid proliferating cancer cells have a high glycolytic activity, while metastatic cancer cells have high OXPHOS activity.[80–82] In general, the fragmented mitochondria (fission state) have less active OXPHOS compared to the tubular mitochondria (fusion state). It can provide glycolytic intermediates as the building blocks for cancer cell proliferation. However, the relationships between mitochondrial dynamics and cellular metabolism are veiled due to complex mechanisms and factors involved such as the cellular environment, cell type, and differences between metabolic cues.[78]

The fission morphology of mitochondria is often observed in tumor cells, which may be related to tumorigenesis.[83] While the underlying mechanisms that regulate

mitochondrial dynamics in cancer remain unclear, some hyperactivated oncogenic signals, such as Ras, Raf, MYC, CDKN2A and p53, can remodel mitochondrial shape and metabolism during tumorigenesis.[84] Primary fibroblasts display fused mitochondria and rely on OXPHOS, and B-RAF^{V600E} mutation-driven melanoma cells contain fragmented mitochondria.[85] Moreover, changes in mitochondrial dynamics/fission status, such as decreased OPA1 expression in HCC, downregulated mitofusin-2 (Mfn2) in human gastric tumors, and upregulated dynamin-related protein 1 (DRP1) in various cancers, have been found in many cancers.[86–88] These results suggest that mitochondrial dynamic changes may play a potential role during tumorigenesis.

Mitochondrial dysfunction contributes to cancer malignant progression

Different types of mitochondrial dysfunction may contribute to metabolic switch and malignant processes involved in cancer progression, including tumorigenesis, metastasis, and chemoresistance.[39] The relationship between mitochondrial dysfunction or tumor environment and metabolic switch is complicated. In addition to mitochondrial dysfunction, acquired mutations can remodel the cancer metabolism, and tumor microenvironment is another factor that regulates cancer metabolism and provides metabolic heterogeneity.[89] Solid tumors encompass highly disorganized normal tissues and numbers of cell types including endothelial cells for blood vessels, stromal fibroblasts, immune cells, and cancer cells. Stromal fibroblasts can recruit immune cells and further affect the development of vascular system.[90] Leaky vessels inefficiently transport nutrients and eliminate cellular metabolism wastes, such as lactate.[91,92] In addition to insufficient nutrients and waste accumulation, hypoxia exists in vasculature uncovered by limited oxygen supply. The hypoxia response leads to metabolism remodeling though enhanced glycolysis and additional lactate deposition.[93] The metabolism remolding of cancer cells by microenvironments and acquired mutations confers a selective advantage for survival and proliferation in the vile tumor microenvironment.[94]

MtDNA copy number changes

Compared to high mtDNA copy number, low mtDNA copy number was found to be associated with poor prognosis in HCC patients.[95] Moreover, a reduced mtDNA copy number was observed in malignant gastric cancer phenotypes, such as ulcerated, infiltrating, and diffuse types (Bormann's type III-IV).[34] Reduced mtDNA copy number was also correlated with older onset age, higher histological grade, and poorer disease-free survival and overall survival rates in breast cancer patients.[96] MtDNA-depleted (long term-ethidium bromide EtBr, an mtDNA replication inhibitor treated and adapted) cancer cells were found to be linked to invasiveness and metastasis through induction of the expression of epithelial-to-mesenchymal transition (EMT) proteins and stemness markers.[97] The mtDNA-depleted prostate cancer cells exhibit cancer stem cell features such as CD44 and ABCG2.[98,99] A reduced mtDNA copy number (such as mutant mitochondrial polymerase γ- or EtBr-mediated) was found to induce an invasive phenotype.[100,101]

However, whether decreased mtDNA copy number contributes to cancer progression is still controversial in some cancers, such as head and neck cancer and esophageal squamous cell carcinoma.[102,103] The alterations of mtDNA copy number required for cancer initiation and progression are tissue specific and complicated. Two ρ^0 murine cancer cells (B16 melanoma and 4T1 breast carcinoma) formed tumors *in vivo* more slowly than mtDNA-sufficient (ρ^+) parental cells. Moreover, the mtDNA copy number could be recovered in derivatives of the originally ρ^0 cells at different stages of malignant progression, such as primary cells at the tumor injection site, circulating tumor cells, and lung metastasis cancer cells.[104] These results suggest that mtDNA-deficient cancer cells can recover mtDNA from host cells, restoring their OXPHOS activities to a level that is sufficient for tumor initiation and progression.

Mitochondrial transcription factor A (TFAM) plays an important role in regulating mtDNA copy number. TFAM is an important mediator of mitochondrial damage-associated molecular patterns and can further regulate inflammation and immunity.[105] TFAM is an important regulator of mtDNA replication. Recently, it was found that a TFAM-mediated increase in mtDNA copy number is important to promote cancer progression by enhancing OXPHOS in microsatellite-stable colorectal cancer.[106] In addition, the TFAM-mtDNA-calcium-cilia and flagella-associated protein 65 (CFAP65)-cytoplasmic phosphoenolpyruvate carboxykinase (PCK1) axis, which is connected to mitochondrial retrograde signaling, affects cancer cell differentiation and proliferation and contributes to cancer progression.[107] Therefore, whether increased or decreased mtDNA copy number contributes to cancer progression is still controversial and may also have tissue-specific trend corresponding to different types of cancers.

Some lines of evidence show that mtDNA-depleted cells (long term-EtBr treated) are resistant to chemotherapeutic agents such as doxorubicin, cisplatin, and etoposide.[108–110] Some underlying mechanisms linking mtDNA copy number alterations in cancer progression have been proposed, such as an increase of manganese superoxide dismutase (MnSOD) and elimination of the effects of chemotherapeutic agents by developing P-glycoprotein-mediated multidrug resistance (MDR) phenotype or activation of mitochondria-to-nucleus retrograde signaling to increase the expression of antiapoptotic genes (including B cell lymphoma-2 (Bcl-2) and pro-survival enzymes such as Akt).[111–115] Moreover, mtDNA copy number alterations (EtBr-treated) may contribute to endocrine therapy resistance in prostate and breast cancer cells.[116,117] MtDNA-depleted prostate cancer cells and breast cancer cells lose their hormone dependence and exhibit tamoxifen and fulvestrant resistance. However, it was reported that a high copy number of mtDNA could be a potential biomarker for predicting unfavorable efficacy of anthracycline treatments in breast cancer patients.[118] The exact role of mtDNA copy

number alterations in cancer treatment resistance needs further investigation.[110,117,119,120]

MtDNA mutations

The incidence of somatic mtDNA D-loop mutations is high in advanced staged cancers such as HCC, gastric, lung and colorectal cancers.[38] In breast cancer patients, the incidence of mtDNA D-loop mutations is associated with old age and lack of hormone receptor (such as estrogen receptor and progesterone receptor) expression. Moreover, mtDNA D-loop mutations are significantly related to poor prognosis in breast cancer patients.[35] Furthermore, several somatic mtDNA mutations in the coding region were identified in breast cancers. The occurrence of these somatic mtDNA mutations is also associated with old age, late stage, and malignant histological grade.[44] These findings suggest that mtDNA somatic mutations may be the biomarkers for breast cancer prognosis.

In chronic lymphocytic leukemia, patients which refractory to conventional therapeutic agents have higher rate of cancer mtDNA mutations than good responder patients.[121] It was also reported that mutant mtDNA (such as mtDNA ATP synthase subunit 6 gene pathogenic point mutation) cybrids confer cisplatin resistance via resistant to apoptosis.[122] Reduced ATP synthase activity contributes to 5-flurouracil resistance in colon cancer cells.[123] Reduced mitochondrial Complex I (NADH dehydrogenase) activity was also found to significantly regulate the aggressiveness of human breast cancer cells via NAD^+/NADH redox balance, mTORC1 activity, and autophagy.[124] Moreover, normal mitochondrial transplantation was found to decrease cell growth, ROS levels, and chemoresistance in breast cancer cells. In addition, replacement of normal mitochondria with mtDNA A8344G-mutated dysfunctional mitochondria abolished the original suppression of cancer cell growth via distinct metabolic remodeling such as switches to the energetic and glycolytic phenotypes.[125] These findings suggest that mtDNA mutation-induced mitochondrial dysfunction or decreased mitochondrial activity may contribute to the malignant progression of various cancers. Interestingly, it was reported that patients with common pathogenic mtDNA mutations and mitochondrial dysfunction do not appear to be at increased risk of cancer compared with the general population.[126] However, this might not rule out that these mtDNA mutations contribute to a vicious cycle of further malignant transformation.[127]

Mitochondrial enzyme defects

FH-deficient renal cancers are often highly aggressive and frequently metastasize even when the tumors are small, resulting in poor clinical prognosis.[128,129] FH deficiency contributes to cancer progression through enhanced invasion and migration in clear cell renal cancers or induced EMT in kidney cancer cells.[130–132] In clear cell renal cancers, low SDH subunit B (SDH-B)-expressing patients have a poorer prognosis than high-expressing patients.[133] Moreover, SDH mutations contribute to cancer progression by promoting EMT cell migration, invasion, and angiogenesis.[134] Low IDH1 expression in breast cancer is significantly correlated with late stage, lymph node metastasis, and poor prognosis.[135] Accumulation of 2-hydroxyglutarate (2-HG) may contribute to poor prognosis and treatment response in acute myeloid leukemia (AML).[136] Glioma-derived IDH2 mutations may contribute to chemoresistance through HIF-1α and β-catenin signaling.[137] Furthermore, low expression of IDH could be observed in doxorubicin-resistant breast cancer cells.[138] However, it was reported that the chemotherapy response is conversely correlated with FH deficiency in gastric cancers.[139] The role of mutations in the tricarboxylic acid cycle (TCA) cycle enzymes in cancer therapy resistance has not been fully investigated.

In gastric cancer, low SIRT3 expression was found to be associated with poor prognosis.[75] Moreover, low SIRT3 expression may contribute to poor prognosis in pancreatic cancers.[140] p53 and p21 may be mediators of the SIRT3-mediated mitochondrial stress response in lung adenocarcinoma or oral carcinoma cells.[141,142] In addition to cancer progression, the loss of SIRT3, which leads to the acetylation of MnSOD and other mitochondrial proteins, has a connection with ROS and the development of luminal B breast cancer and may contribute to endocrine therapy resistance.[143]

Mitochondrial dynamic changes

The inhibition of mitochondrial fragmentation by DRP1 knockdown can increase genomic instability and decrease migration and invasion by cellular stress in breast cancer cells.[144,145] Impaired mitochondrial fission can cause mtDNA mutation-mediated mitochondrial dysfunction and deregulation of redox homeostasis. Inhibition of mitochondrial fission can be a potential modality for enhancing cancer cell apoptosis and increasing sensitivity to cancer therapy.[145,146] Some oncogenes are responsible for fragmented mitochondria in cancer cells through the RAS-RAF-MEK-ERK (MAPK) pathway. DRP1 can be phosphorylated by extracellular-signal-regulated kinase 2 (ERK2) on Ser616 and is required for mitochondrial fission and tumor growth in RAS-transformed tumors. This result indicates that MAPK activation and consequent mitochondrial fragmentation are needed in tumors expressing oncogenic RAS.[87] On the other hand, tissue from tumor metastasis to lymph nodes was found to highly express DRP1 compared to the original tumor or normal/adjacent tissue.[144] Moreover, hormones such as androgen and estradiol have a strong influence on mitochondrial dynamics. These findings suggest that targeting mitochondrial dynamics for cancer progression in hormone-related malignancies may be a newly effective treatment strategy.[147,148]

Mitophagy, which is a specific type of autophagy for damaged, dysfunctional or unhealthy mitochondria, can maintain mitochondrial dynamics by the lysosome-mediated pathway. Several canonical mitophagy pathways have been proposed, such as PTEN-induced putative kinase 1 (PINK1)/Parkin, bcl-2/adenovirus E1B protein-interacting protein 3 (BNIP3)/NIX, and FUN14 domain-containing 1 (FUNDC1).[149] Several lines of evidence have

shown that inhibition of mitophagy could contribute to increased efficacy of chemotherapy.[150,151] Moreover, chemoresistance in some cancer cells may be induced by increased mitophagy.[152,153] However, the mitochondrial fusion status may contribute to resistance to cisplatin therapy.[154] The role of mitophagy in cancer progression is controversial.[155,156] The mitochondrial stress response that occurs in response to changes in mitochondrial dynamics is very complicated, and the detailed regulatory mechanism for cancer progression and/or therapy resistance remains to be further investigated.

Mitochondrion-derived molecules are involved in mitochondrial retrograde signaling pathway for cancer progression

Mitochondrial dysfunction can produce various retrograde signals. Through these signals, cells can regulate cellular homeostasis and protect cells against environmental stresses by retrograde regulation of the expression of nuclear genes.[157] The nature of retrograde signals can vary depending on their trigger. ROS, Ca^{2+}, and oncometabolites are common mitochondrion-derived molecules.[158] Other mitochondrion-derived molecules, such as exported mtDNA, exported mitochondrial double-stranded RNA (mt-dsRNA), humanin and MOTS-c, are also proposed to be involved in the retrograde signaling pathway.[159–162]

ROS and Ca^{2+}

ROS are common byproducts of OXPHOS that are often elevated due to a defective electron transport chain; ROS directly affect redox homeostasis and act as signaling molecules in a number of cellular processes under normal or stress environments.[163] In mammalian cells, increased ROS activate retrograde signaling to activate detoxification enzymes or increase antioxidant ability by nuclear factor erythroid 2-related factor 2 (NRF2).[164] In addition, ROS can compensate for increased mitochondrial biogenesis by activating the JNK–PGC1α pathway and promoting mitochondrial Complex II phosphorylation.[165,166] In cancer cells, mitochondrial ROS contribute to promoting cell growth and survival via the nuclear factor-κB (NF-κB) pathway.[167] On the other hand, mitochondria are important organelles responsible for calcium storage and homeostasis.[168] Mitochondrial stressors such as mtDNA mutation, OXPHOS disruption, and mitochondrial membrane potential uncoupling can trigger Ca^{2+} release from mitochondria. Free cytosolic Ca^{2+} can activate the NF-κB, Jun N-terminal kinase (JNK), and p38 MAPK pathways. Moreover, Ca^{2+} can increase the expression of various transcription factors, such as CREB, early growth response protein 1 (EGR1), ATF2, CCAAT/enhancer-binding protein-δ, and CHOP.[169,170] Calcium retrograde signaling not only contributes to mitochondrial adaptation but is also involved in calcium homeostasis, insulin regulation, glucose metabolism remodeling, and cell proliferation.[158]

Mitochondrial stress induced by mitochondrial inhibitor (such as oligomycin)-decreased mitochondrial activity enhances the migration of gastric cancer cells via ROS-mediated retrograde signaling.[42] Mitochondrial inhibitors (such as oligomycin and antimycin A)-induced ROS-β5-integrin retrograde signaling plays an important role in promoting cell migration.[171] In addition to metastasis, ROS are involved in mitochondrial stress (by mitochondrial inhibitors)-induced chemoresistance in gastric cancer cells.[172] Moreover, ROS- and calcium-mediated expression of amphiregulin (AR) is important for mitochondrial stress (by mitochondrial inhibitors-decreased mitochondrial activity or interfering mtDNA transcription and translation)-induced chemoresistance and migration in HCC cancer cells.[173] ROS are also involved in defective SIRT3-mediated cancer progression.[141,142] Furthermore, mitochondrion-derived ROS mediate the regulation of vascular endothelial growth factor (VEGF), which may be one of the possible mechanisms of tumorigenesis and metastasis regulated by MAPK-mediated mitochondrial fission. These results indicate that mitochondrial dysfunction-mediated ROS and Ca^{2+} changes contribute to cancer progression.

Oncometabolites

The mutations of FH and SDH, two nuclear genome-encoded enzymes of the citric acid cycle, may lead to the accumulation of fumarate and succinate. These two metabolites have been shown to lead to malignant transformation and tumorigenesis.[174–176] 2-HG accumulates in response to defects in NADP-dependent IDH 1 (cytosolic) and 2 (mitochondrial) in different cancers.[69,177] Moreover, mutations of IDH in cancer strongly implicate metabolism remodeling during tumorigenesis.[178] Fumarate, succinate, and 2-HG are thus thought to be oncometabolites. Accumulation and subsequent release of fumarate and succinate from mitochondria might lead to HIF1 stabilization and α-ketoglutarate-dependent dioxygenase inhibition-mediated DNA and histone modifications, which promote cancer progression by EMT, angiogenesis, and cellular glucose or energy metabolism remodeling.[179–181] 2-HG accumulation and release from mitochondria contribute to the malignant phenotype by affecting DNA demethylation and promoting epigenetic changes. Furthermore, 2-HG might inhibit the activity of Complex IV/V and subsequently induce the mitochondrial stress response, which is responsible for deregulating cellular energetics.[182,183] These results indicate that oncometabolites such as fumarate, succinate, and 2-HG are involved in retrograde signaling for cancer progression.

MtDNA and mitochondrial double-stranded RNA

The inflammasome plays an important role in a myriad of acute/chronic inflammatory and degenerative diseases.[184] The inflammasome is composed of a set of intracellular protein complexes that enable autocatalytic activation of inflammatory caspases and drive some cytokine secretion. Cytosolic oxidized mtDNA was identified to activate the NLRP3 inflammasome complex.[162] The NLRP3 inflammasome is unique and can be triggered by a number of stresses.[184] Persistently aberrant NLRP3 signaling contributes to several immune disorders and degenerative

diseases, such as autoimmune disorders, gout, osteoarthritis, Alzheimer's disease, type 2 diabetes, atherosclerosis, lupus, macular degeneration, and cancer.[185,186] Circulating mtDNA inhibited the production of proinflammatory cytokines, horizontal transfer of mtDNA from tumor cells to surrounding immune cell-activated apoptosis in immune cells, and inappropriate sensing of mtDNA leading to dysfunction of the host immune system, consequently contributing to cancer progression.[187] Mitochondrial double-stranded RNA exported from mitochondria was recently demonstrated to engage an MDA5-driven antiviral signaling pathway that triggers a type I interferon response with antiviral effects.[161] Synthetic dsRNA may potentially be a new immunotherapy for cancer treatment.[188] However, the exact role of mitochondrial double-stranded RNA in cancer progression is still unclear.

Humanin and MOTS-c

Some mitochondrial-derived peptides are encoded from the mitochondrial genome. Humanin is the first reported and better characterized mitochondrial-derived peptide that provides protective effects against various stresses.[189] Humanin is a 24-amino acid short peptide originally isolated from a cDNA library that was screened for survival factors in a study about Alzheimer's disease (AD).[190] It is transcribed by a part of the mitochondrial MT-RNR2 gene, which encodes 16S mitochondrial ribosomal RNA (16S rRNA). Humanin expression can be triggered by mitochondrial stressors such as serum deprivation and chemotherapy or inhibited by steroid hormones such as estrogen. In cancer, humanin was initially proposed to be a potential oncopeptide.[191] ERK1/2 and STAT3 may be humanin downstream targets in the development of several types of tumors, such as glioblastoma, triple-negative breast cancer, and pituitary tumors.[189] Moreover, evidence has shown that humanin contributes to chemoresistance and cancer aggressiveness.[192,193]

Mitochondrial open reading frame of the 12S rRNA type-c (MOTS-c), which is a 16-amino acid peptide encoded by the mitochondrial 12S rRNA gene, is another mitochondrial-derived peptide. It was originally found in the *in silico* search for potential short open reading frames (sORFs) within the human 12S rRNA and was then identified to have a biological function in metabolic homeostasis.[159,194] The physiological function of MOTS-c can be exhibited by the relief of metabolic syndromes such as obesity, insulin resistance, and Q fever/chronic fatigue syndrome.[159,195,196] Initially, MOTS-c was demonstrated to target the one-carbon pool and *de novo* purine synthesis pathways to increase 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) levels and activate AMP-activated protein kinase (AMPK).[159] It can stimulate glucose utilization and lactate production coupled with reduced mitochondrial oxygen consumption as well as increased fatty acid utilization, which suggests that MOTS-c can maintain metabolic homeostasis for the regulation of obesity, diabetes, exercise, and longevity.[159] Increased intracellular ROS in response to metabolic stress may mediate the translocation of MOTS-c to the nucleus via AMPK-dependent regulation.[197] Moreover, MOTS-c is responsive to retrograde signaling via interaction with multiple stress-response transcription factors, including nuclear factor erythroid 2-related factor 2 (NFE2L2/NRF2) and activating transcription factor 1 and 7 (ATF1/ATF7). Metabolic dysfunction and remodeling are characteristics of cancer cells. Mitochondrial dysfunction can down-regulate HIF-1α via the activated AMPK pathway in HCCs.[198] Hence, this may provide a potential link between MOTS-c and cancer progression. There is still much to be unveiled about metabolic rewiring via these mitochondrion-derived molecules in tumor formation and malignant progression.

Mitochondrial unfolded protein response in cancer progression

The mitochondrial proteome contains more than a thousand mitochondrial proteins that are encoded by nuclear and mitochondrial genomes. Mitochondrial biogenesis and function are dependent on the maintenance of protein import pathways and the protein-folding circumstances. Deregulating mitochondrial proteostasis can induce mitochondrial stress and negatively affect mitochondrial function. Mitochondrial stress in response to accumulation of misfolded mitochondrial proteins in the mitochondrial matrix, impairment of the protein quality control system, mitonuclear imbalance or inhibition of the electron transport chain (ETC) can induce the mitochondrial unfolded protein response (UPR^{mt}).[199] Cells usually use impaired protein as a sensor for mitochondrial dysfunction to activate the specific UPR^{mt}, a mitochondrial stress response. It can activate an adaptive transcriptional program that promotes mitochondrial function recovery, metabolic adaptations, and innate immunity.[200]

The UPR^{mt} can activate the transcription of the CCAAT-enhancer-binding protein homologous protein (CHOP) gene, dimerize with CCAAT/enhancer-binding protein β (C/EBP-β), and bind to the promoters of UPR^{mt}-responsive genes. It can further regulate mitochondrial quality control proteins via molecular chaperones and proteases.[201] UPR^{mt}-induced mitochondrial chaperones heat shock protein 60 (hsp60) and mthsp70, which promote protein folded and prevent aggregated formation are involved in mitochondrial recovery program.[200] UPR^{mt}-activated AAA proteases such as Lon and ClpXP are responsible for removing damaged mitochondrial proteins.[200] Moreover, the UPR^{mt} can promote mitochondrial biogenesis and function via elevation of iron–sulfur cluster and ubiquinone synthesis which is required for OXPHOS complex biogenesis. Furthermore, UPR^{mt} can promote clearance of defective mitochondria by mitochondrial dynamic, such as DRP1.[200] These transcriptional outputs of the UPR^{mt} mediate its recovery of damaged mitochondria.

The UPR^{mt} has been extensively investigated in *C. elegans* model system. Digestion of unfolded or unassembled mitochondrial proteins into peptides by the matrix protease ClpP can activate UPR^{mt} through efflux of short peptides to cytoplasm by HAF-1 transporter.[202]

Accumulation of digested short peptides induces a transcriptional response by activating transcription factor associated with stress 1 (ATFS-1) in worms.[203] ATFS-1 contains mitochondrial and nuclear targeting signals. ATFS-1 is normally imported into mitochondria and degraded by the Lon protease. Under mitochondrial stress, the import of ATFS-1 to mitochondria is attenuated. ATFS-1 will be translocated to the nucleus along with two other factors, DVE-1 and ubiquitin-like 5 (UBL-5) to regulate the gene expressions of mitochondrial chaperones (such as *hsp*-6, *hsp*-60, and DNaJ domain 10 (*dnj*-10)) and proteases (such as *ymel*-1) for mitochondrial quality control and restoring proteostasis. Moreover, it can positively regulate the DRP-1, glycolytic genes such as *gpd*-2, detoxification genes such as *skn*-1, and translocase of the inner membrane 23 (TIM23). Furthermore, it can negatively regulate the expression of other nuclear mitochondrial genes, such as TCA cycle enzymes and ETC subunits.[158,204,205] In addition to regulating genes involved in mitochondrial proteostasis, the UPR^{mt} also mediates homeostasis through metabolic remodeling from mitochondrial OXPHOS to cytoplasmic glycolysis.

In mammalian cells, UPR^{mt} was initially introduced by the overexpression of the mitochondrial matrix-localized misfolded mutant ornithine transcarbamylase.[201] The transcription factor ATF5 as the mammalian ortholog of ATFS-1 was recently identified.[206] Both ATF4 and ATF5 have been considered for harboring bZip domain homologous to ATFS-1. In addition, evidence showed that ATF5 have a putative, but relatively weak mitochondrial targeting sequences (MTS). However, multi-omics analysis identifies ATF4 as a key regulator of UPR^{mt}, not through the canonical ATF5 in mammalian cells.[207] The key regulator of UPR^{mt} in mammalian cells remains controversial.

In addition to the first identified regulation pathway, CHOP-ATF5, a number of mitochondrial chaperones and proteases, such as ClpP, hsp10, and hsp60, are involved in the UPR^{mt}. In addition, several mechanisms have been proposed, such as those involving SIRT7, estrogen receptor α (ERα), and the SIRT3 response pathway.[208] The UPR^{mt} contributes to mitoprotective outcomes by regulating antioxidant ability, proteostasis, OXPHOS, mitochondrial biogenesis, mitophagy, and so on. Recently, mitohormesis was introduced as a response to mitochondrial stress in the hormetic zone, which is composed of low-level exposure mitochondrial stress and induces favorable biological responses.[209–211] Mitohormesis can induce cancer invasion/metastasis and poor clinical outcomes through the UPR^{mt}.[211] Moreover, UPR^{mt} has been reported to involve the activation of ERα, and the UPR might play an important role in aromatase inhibitor-resistant breast cancer cells.[212,213]

ATF5 is up-regulated in numbers of cancers and is related to apoptosis resistance.[214] The synthetic cell-penetrating dominant-negative ATF5 peptide provides the antitumor activity against treatment-resistant cancers by monotherapy or in combination therapy.[215] This is relevant considering that ATF5-mediated UPR^{mt} might play an important role in cancer progression. Moreover, targeting to other UPR^{mt} downstream targets such as LonP1 by obtusilactone A and sesamin compounds from *Cinnamomum kotoense*, ClpP by genetic or chemical inhibition and hsp60 by genetic ablation are helpful against numbers of cancers.[216–218] Mitochondrial stress-induced UPR^{mt} is important to cancer progression. In addition, mitochondrial ROS are important for UPR^{mt}-induced mitoprotective pathways. These lines of evidence suggest that UPR^{mt} is one of the mitochondrial stress responses and is involved in retrograde mitonuclear communication for cancer progression.

Integrated stress response is involved in mitochondrial stress response and contributes to cancer progression

Depending on the severity and nature of the stress, the integrated stress response (ISR) modulates various cellular functions to adapt to stress. The core of ISR is the phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) and activation of the activating transcription factor-4 (ATF4) pathway. The eIF2α belongs to the multimeric eIF2 complex and is responsible for cap-dependent protein translation.[219] Four eIF2α kinases have been identified to be responsible for eIF2α phosphorylation: PKR-like endoplasmic reticulum kinase (PERK), general control nonderepressible 2 (GCN2), protein kinase R, and heme-regulated eIF2α kinase.[219–222]

Phosphorylated eIF2α inhibits cap-dependent protein translation under stress conditions and allows cells to adapt stress through upregulation of ATF4-translation and subsequent activation of its downstream genes.[223] The ISR protects against intrinsic/extrinsic cellular stress (such as endoplasmic reticulum stress, hemoglobin deficiency, nutrient deficiency, viral infection, or hypoxia) by regulating transporters, antioxidant systems, chaperones, and so on.[223–225] The eIF2α-ATF4 pathway not only maintains cellular redox homeostasis but also regulates cellular metabolism and nutrient uptake.[226,227] On the other hand, it can induce cell death through activation of proapoptotic bcl-2 family proteins or death receptor 5 via the ATF4-CHOP pathway.[228–230] Nutrient deprivation can also induce cell necrosis through the ATF4-dependent ISR pathway.[231] ISR encompasses a dual role in cellular homeostasis.[232,233]

The ISR has been proposed to be involved in mitochondrial-nuclear communication and thus responsible for cellular homeostasis and lifespan.[158] ATF4 has been identified as a key regulator of the mitochondrial stress response in mammalian cells.[207] Mitochondrial stress in response to arsenic or doxycycline can decrease mitochondrial function and reprogram gene expression to maintain mitochondrial protein homeostasis through the eIF2α-ATF4 pathway.[234–236] PERK and GCN2 were recently identified to be involved in the mitochondrial stress response.[237–239] Moreover, ETC dysfunction, ROS elevation and mitochondrial unfolded protein stress can activate GCN2, PERK, or HRI, depending on clinical situation.[158]

The ISR is an important way by which tumor cells adapt to environmental stress, and it contributes to tumor growth.[240] ATF4 expression is higher in tumor tissues compared to normal tissues.[240,241] Evidence has shown that the eIF2α-ATF4 pathway is critical for tumor cell survival and

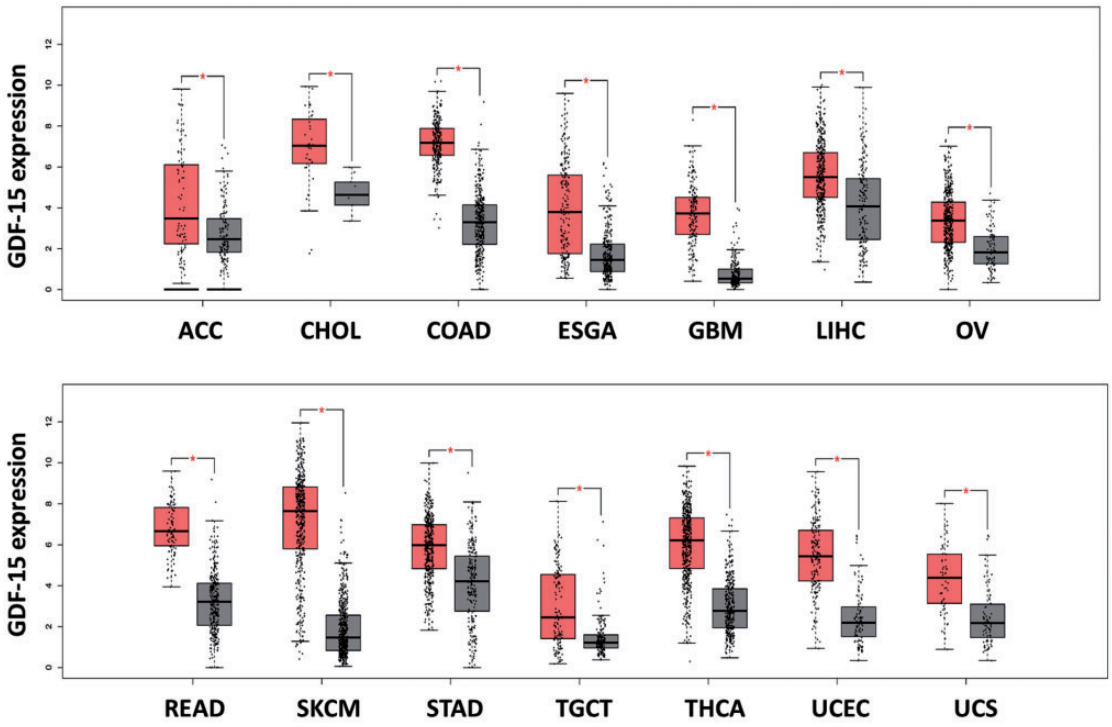

Figure 1. The gene expression of GDF-15 in tumors and normal tissues in several cancers. The RNA sequencing expression data were obtained from the TCGA and the GTEx projects. The gene expression of GDF-15 in normal tissues (gray box) and tumor tissues (red box) from several cancers was analyzed by box-plot. The box-plot was generated by the GEPIA website and software (http://gepia.cancer-pku.cn/).[270] |Log2FC| cutoff: 1; *P*-value cutoff: 0.01 (ACC: adrenocortical carcinoma, tumor (T) number: 77, normal (N) number: 128; CHOL: cholangiocarcinoma, T number: 36, N number: 9; COAD: colon adenocarcinoma, T number: 275, N number: 349; ESGA: esophageal carcinoma, T number: 182, N number: 286; GBM: glioblastoma multiforme, T number: 163, N number: 207; LIHC: liver hepatocellular carcinoma, T number: 369, N number: 160; OV: ovarian serous cystadenocarcinoma, T number: 426, N number: 88; READ: rectum adenocarcinoma, T number: 92, N number: 318; SKCM: skin cutaneous melanoma, T number: 461, N number: 558; STAD: stomach adenocarcinoma, T number: 408, N number: 211; TGCT: testicular germ cell tumors, T number: 137, N number: 165; THCA: thyroid carcinoma, T number: 512, N number: 337; UCEC: uterine corpus endometrial carcinoma, T number: 174, N number: 91; UCS: uterine carcinosarcoma, T number: 57, N number: 78). (A color version of this figure is available in the online journal.)

proliferation in response to nutrient deprivation.[242] In addition, cancer cells with knockdown of ATF4 formed fewer tumor lesions that were smaller and had slower growth compared with the large burden and rapid growth of control tumor lesions. ATF4 promotes cancer metastasis by induction of heme oxygenase 1-mediated reducing anoikis of cancer cells.[243] Moreover, ATF4 is involved in c-Myc oncogene-driven malignant progression through uncharged transfer RNA-mediated GCN2 activation.[244] These results indicate that ISR is critical for the initiation and progression of cancer.

The ATF4 signaling pathway includes several downstream targets, such as apoptotic genes (Bcl-2, NOXA/PUMA, BIM), adaptive genes (such as amino acid transporters, metabolic enzymes, redox balance, endoplasmic reticulum chaperones), and several recycling of cellular material-related genes (such as autophagy genes, REDD1/DDIT4/SESN2, and GADD34).[245]

SLC7A11 (xCT), a downstream protein in the ATF4 pathway, is involved in the x_c^- system and is responsible for cysteine uptake and supports cellular glutathione (GSH) synthesis.[246] Mitochondrial inhibitor-induced mitochondrial stress was found to induce chemoresistance via the ROS-mediated GCN2-ISR-xCT pathway.[172] Increased antioxidant ability in response to GSH generation is responsible for the ISR-xCT-mediated chemoresistance in gastric cancer cells.[247] xCT is also important for cystine dependency in triple-negative breast cancer cells.[248] Moreover, the increased expression of xCT contributes to glucose and glutamine dependency via reduced metabolic inflexibility and imbalance of redox status.[249–251] Therefore, the ATF4-xCT pathway may play a critical role in the metabolism remodeling and therapy resistance of cancer cells.

On the other hand, cysteine starvation-induced high ROS production and mitochondrial stress were found to induce necroptosis and ferroptosis via the GCN2-ISR-CHAC1 pathway in triple-negative breast cancer cells.[252] The ISR can result in adaptive or deleterious effects depending on the extent of the mitochondrial changes. Since cancer cells need abundant energy and macromolecular supplies for sustainable cell growth, most cancer cells have tolerable levels of mitochondrial dysfunction and acquire an ability to adapt to cancer microenvironments via the mitochondrial stress response. Therefore, the mitochondrial stress response may be a treatment target for cancer patients.

Until 2011, no reliable biomarker for mitochondrial disorders or mitochondrial dysfunction was identified. The serum fibroblast growth factor 21 (FGF-21) is identified as a useful biomarker for the screening and diagnosis of muscle-manifested mitochondrial disorders.[253] The diagnostic process of mitochondrial disorders is proposed such as clinical assessment, FGF-21 level, sequencing of

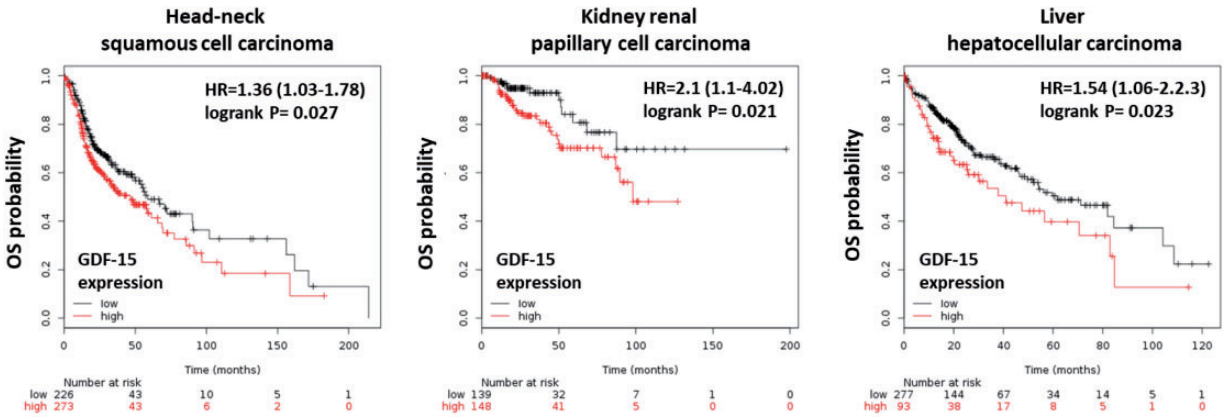

Figure 2. Kaplan–Meier survival analyses for GDF-15 expression on overall survival (OS) in several cancers. The RNA-seq data were collected from several databases, including GEO, EGA, and TCGA. The Kaplan–Meier survival analysis (overall survival) was analyzed by the KM plotter website and software (https://kmplot.com/analysis/).[271] Kaplan–Meier survival analyses showed that high expression of GDF-15 is a poor prognostic factor in head-neck squamous cell carcinoma, kidney renal papillary cell carcinoma, and liver hepatocellular carcinoma. (A color version of this figure is available in the online journal.)

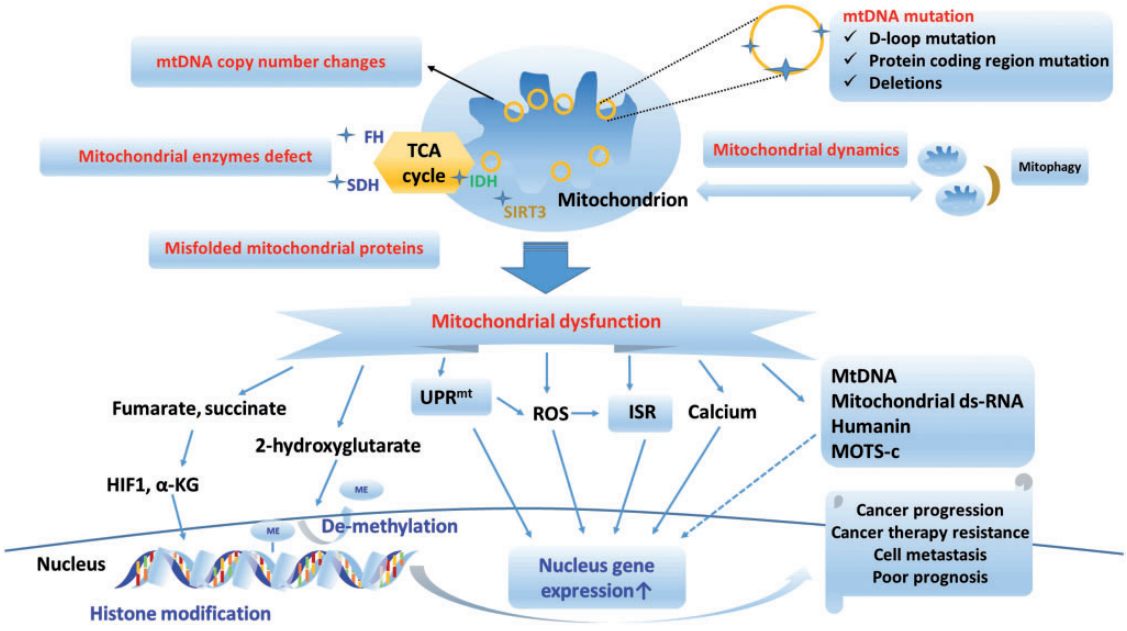

Figure 3. Summary of retrograde signaling pathways and mitochondrial stress responses in mitochondrial stress-induced cancer progression and carcinogenesis. Several mitochondrial alterations, such as mtDNA copy number changes, mtDNA mutations, mitochondrial enzyme defects, and mitochondrial dynamic changes, can induce mitochondrial dysfunction in cancer cells. Several retrograde signaling pathways, such as ROS, calcium, oncometabolites, exported mtDNA/mt-dsRNA, humanin, MOTS-c, UPR^{mt} and ISR, are involved in the mitochondrial stress responses. The retrograde mitochondrial stress response can affect several nuclear gene expressions and plays an important role in cancer progression. (A color version of this figure is available in the online journal.)

nuclear DNA, and with/without biopsy, which can clinically be used for differential diagnosis of about 70–80% of suspected mitochondrial disorders.[254] Recently, the evidence showed that ISR is involved in FGF-21 regulation.[255,256] Although FGF-21 might be used for early diagnosis of liver cancer or renal cancer and might be a biomarker for predicting tumor progression, the understanding the role of FGF-21 in cancer initiation and progression is limited.[257–259] The gene expression of FGF-21 in tumors part is not increased compared to the normal counterpart in cancers by the gene expression profiling interactive analysis (GEPIA) website (http://gepia.cancer-pku.cn/).

On the other hand, evidence showed that growth differentiation factor 15 (GDF-15) has greater sensitivity and specificity than FGF-21 for the diagnosis and/or the monitoring of disease progression of mitochondrial disorders in adults and children.[260] GDF-15, a member of the transforming growth factor beta (TGF-β) superfamily, is also regulated by ISR and may be a useful biomarker for mitochondrial dysfunction.[255,256,260,261] The expression of GDF-15 is often elevated in response to cellular stress such as inflammation, cancer, cardiovascular diseases, obesity, kidney disease, and brain disease.[262] High gene and protein expression levels of GDF-15 have been identified in several cancers [263] (Figure 1), but the findings regarding the

function of GDF-15 in cancers are limited and controversial.[262] High GDF-15 expression is a poor prognostic factor in head-neck, kidney, and liver cancers (Figure 2). In addition, GDF-15 was found to be associated with gastric wall invasion and lymph node metastasis in diffuse-type gastric cancers.[264] It was also suggested that the GDF-15-activated Akt pathway may contribute to proliferation and migration in cervical and pancreatic cancer cells.[265,266] Moreover, it was suggested that circulating GDF15 may be a powerful biomarker for bone metastasis in several cancers.[267] However, GDF15 can inhibit proliferation and bone metastasis in lung adenocarcinoma cancer cells.[268] Low expression of GDF15 is associated with a poor prognosis in nonsmall-cell lung cancer (NSCLC) patients.[269] The role of GDF-15 in cancer progression is still unclear and may depend on cell-type specificity.

Conclusion

Numbers of endogenous or exogenous stresses can induce mitochondrial dysfunction. However, not all of mitochondrial dysfunction can produce mitohormesis to adaptations. Mild mitochondrial stress can actually protect cells from detrimental outcomes of subsequent larger stress. Cancer cells with Warburg effects characteristic or mitochondrial dysfunction (in hormesis) might contribute to adaption of tumor microenvironments or supporting for cell proliferation through several stress response pathways.

Herein, we summarize that mitochondrial dysfunction (non-lethal condition)-mediated mitochondrial stresses contribute to tumor malignant phenotype and increased ability of environmental adaption through increasing metastatic/invasion activity and promoting therapy resistance. Mitochondrial dysfunction-mediated stress response might provide the metastatic/invasion activity through EMT, stemness activity remodeling, and increased antioxidant ability for reducing anoikis. Moreover, mitochondrial dysfunction-mediated increasing detoxification enzymes, such as MnSOD, P-glycoprotein-mediated MDR, and xCT-mediated GSH elevation, might contribute to chemoresistance. Furthermore, ISR-activated xCT is important for glucose metabolism remodeling and dependency. This might provide the tumor heterogeneity such as more sensitive to nutrient demand through mitochondrial dysfunction.

Mitochondria are responsible for cell homeostasis. Several mitochondrial stresses are induced by mtDNA mutation, mitochondrial enzyme defects, mitochondrial dynamic changes, and unfolded mitochondrial proteins in cancers. Mitochondrial stress impairs mitochondrial function and induces cancer progression via various mitochondrial stress responses and retrograde signaling. The UPR^{mt}, the ISR, and mitochondrial-derived molecules have recently been proposed to be involved in the mitochondrial-nuclear signaling pathway. Nondeleterious mitochondrial dysfunction can activate the mitochondrial stress response and play an important role in cancer progression. Several retrograde signaling pathways and mitochondrial stress responses contribute to cancer progression (Figure 3). Therefore, targeting the regulatory pathway of the mitochondrial stress response may be a potential therapeutic strategy for addressing cancer progression or therapy resistance in the future.

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