

REVIEW

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Mitochondrial dysfunction, UPR^{mt} signaling, and targeted therapy in metastasis tumor



Rajendiran Keerthiga¹, De-Sheng Pei^{2*} and Ailing Fu^{1*}

Abstract

In modern research, mitochondria are considered a more crucial energy plant in cells. Mitochondrial dysfunction, including mitochondrial DNA (mtDNA) mutation and denatured protein accumulation, is a common feature of tumors. The dysfunctional mitochondria reprogram molecular metabolism and allow tumor cells to proliferate in the hostile microenvironment. One of the crucial signaling pathways of the mitochondrial dysfunction activation in the tumor cells is the retrograde signaling of mitochondria-nucleus interaction, mitochondrial unfolded protein response (UPR^{mt}), which is initiated by accumulation of denatured protein and excess ROS production. In the process of UPR^{mt}, various components are activated to enhance the mitochondria-nucleus retrograde signaling to promote carcinoma progression, including hypoxia-inducible factor (HIF), activating transcription factor ATF-4, ATF-5, CHOP, AKT, AMPK. The retrograde signaling molecules of overexpression ATF-5, SIRT3, CREB, SOD1, SOD2, early growth response protein 1 (EGR1), ATF2, CCAAT/enhancer-binding protein-d, and CHOP also involved in the process. Targeted blockage of the UPR^{mt} pathway could obviously inhibit tumor proliferation and metastasis. This review indicates the UPR^{mt} pathways and its crucial role in targeted therapy of metastasis tumors.

Keywords: Mitochondrial unfolded protein response UPR^{mt}, Retrograde signaling, Mitohormesis, Hypoxia-inducible factor (HIF), Integrated stress response (ISR), Cytosolic heat shock response (HSR)

Background

Mitochondria are essential cellular organelle accountable for crucial cellular pathways such as ATP generation through oxidative phosphorylation, calcium homeostasis, tricarboxylic acid cycle (TAC), innate immunity production, β -oxidation, proteostasis, lipid synthesis, urea cycle, and nucleotide metabolism [1, 2]. These cellular pathways of various mitochondrial functions are tracked to study the retrograde response to recover the organelle from the stress process. The retrograde responses are responsible for gene transcription and protein synthesis to initiate organelle protection [3]. Mitochondrial dysfunction can produce an aggregation of unfolded

proteins when mitochondria are suffered from mtDNA mutation, change in mtDNA number, mitochondrial stress, elevated ROS production, and reduction in mitochondrial number. Henceforth, cells activate a transcriptional response to extend the cell's survival, repair, and rescue the dysfunctional mitochondria. This transcriptional response produced in the mitochondria is specified as mitochondrial unfolded protein response (UPR^{mt}). UPR^{mt} is currently considered an effective target for tumor theranostics because it plays a crucial role in tumor proliferation and metastasis [4, 5].

The mitochondrial stress which induces UPR^{mt} is due to reduction of mitochondrial DNA (mtDNA), deterioration of mitochondrial ribosome, increased reactive oxygen species level (ROS), oxidative phosphorylation disorder (OXPHOS), increased glucose utilization [6, 7]. UPR^{mt} contemplates the mitochondrial proteostasis and reacts to the stress produced inside the mitochondria by

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contemporizing the mitochondrial genome and nuclear genomes to produce quality mitochondrial proteome [8, 9]. The quality mitochondrial proteomes for the organelle's recovery are produced by two elementary classes of proteins (i) chaperones (ii) proteases. The proteins play a crucial role in UPR^{mt} by synchronizing mtDNA and chaperones to deliver a quality proteomic genome. Because of the importance of UPR^{mt} in tumor progression and proliferation, and UPR^{mt} inhibition in tumor theranostics and combined drug therapy, this review is intended to study the specific cellular pathways and mechanisms producing UPR^{mt} in the process of tumor proliferation and metastasis.

Signal transport mediated by UPR^{mt}

The human genomic mitochondria transcribe 22 tRNA, 2 rRNA, and 13 essential proteins, which encodes all four core complexes, namely I, III, IV, and V of the electron transport chain (ETC). Around 99% of the mitochondrial genome proteins of the ETC are transcribed through the

nuclear genome. Nuclear DNA encodes the proteome liable for the conservation, replication, and transcription of the mitochondrial genome. For instance, nuclear DNA encoded POLRMT polymerase transcribes the mitochondrial genome [10]. The protein quality control (PQC) network chaperones and proteases on increased mitochondrial proteomic stress induce mitochondria-to-nuclear signaling crosstalk, and one of the crucial factors is UPR^{mt}. The UPR^{mt} signal can be activated by various factors, including hypoxia, environmental stress, mtDNA mutation (Fig. 1). Due to its important function in maintaining cell homeostasis, dysregulated UPR^{mt} metabolism leads to the pathogenesis of ischemic diseases, heart diseases, aging, neurogenerative disorders, lung disease, and tumors.

The accumulation of enormous ROS perturbs the mitochondrial stress generated through the ETC. NADH ubiquinone oxidoreductase (complex I) and ubiquinol cytochrome c oxidoreductase (complex III) of ETC directly produce stress by interrupting the structure

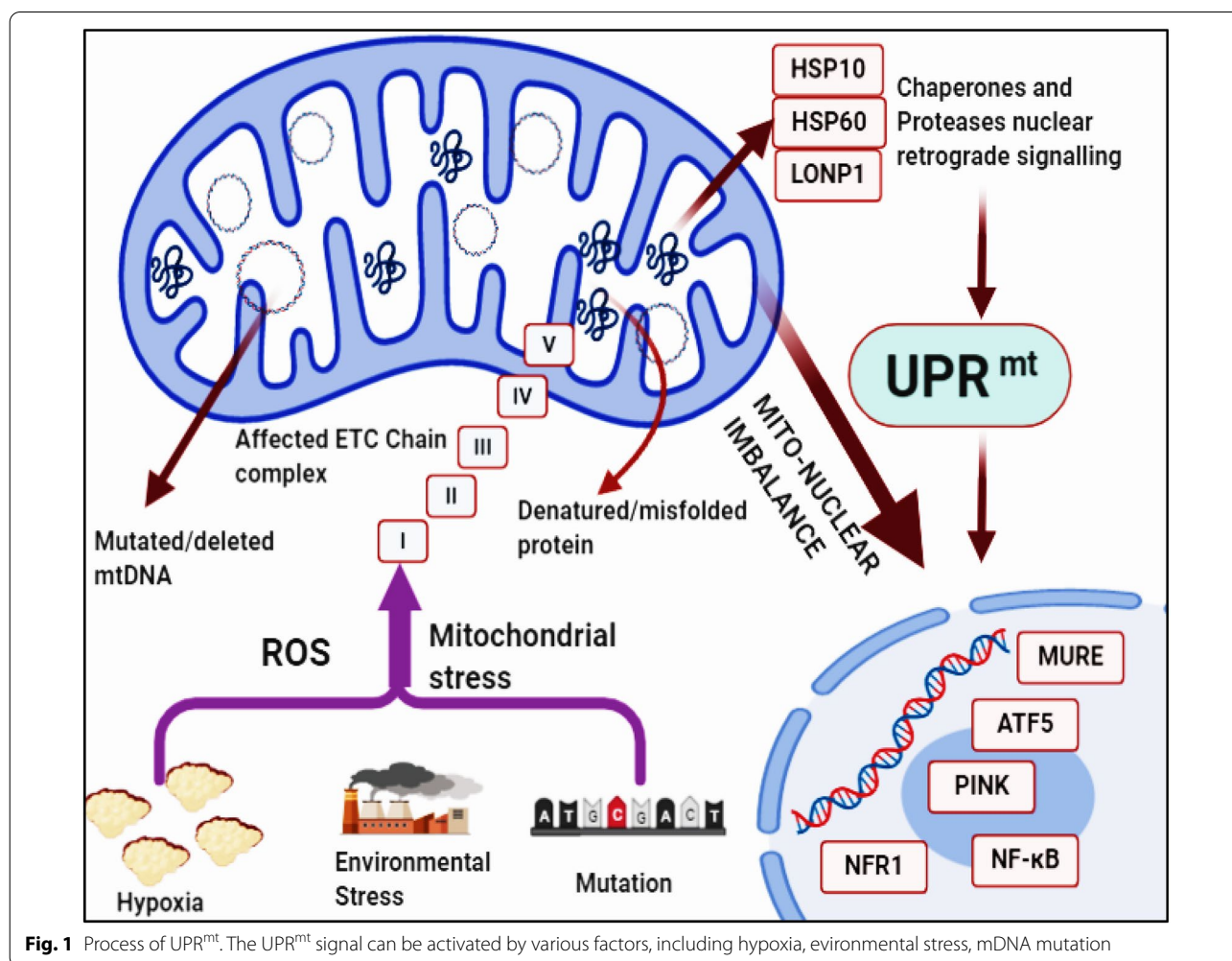


Fig. 1 Process of UPR^{mt}. The UPR^{mt} signal can be activated by various factors, including hypoxia, environmental stress, mtDNA mutation

and the folding mechanism of the proteins [11, 12]. The mitochondrial cytosol heat response (HSR) is induced through the heat shock transcription factor (HSF) by producing cytosolic chaperones, which causes denaturation and misfolding of proteins in mitochondria. Among the two crucial classes of protein Hsp10, Hsp60 and mtHsp70, chaperones and LONP1 proteases hold a critical performance for the UPR^{mt}. The mtHsp70 prevents the folded protein's aggregation and is responsible for the translocation of polypeptide through the matrix with associated PAM (Presequence translocase associated motor) subunits [13]. The AAA proteases (ATPase associated cellular activities), namely ClpP and LONP1, degenerate the oxidized and misfolded proteins [14]. Then paraplegin (SPG7) and YEML1 arrest the respiratory chain protein misfolding inside the mitochondrial membrane matrix.

Signal cascade of UPR^{mt} in metastasis tumors

In tumor cells, the mitochondria's activity is dysregulated due to denatured protein, enhancing the prolonged survival and proliferative advantages of tumor cells, causing

aggressive malignancies and theranostic resistance [15, 16]. The mitochondrial dysfunction and UPR^{mt} of tumor cells include hypoxia-inducible factor (HIF), proliferative stress, integrated stress response (ISR), and cytosolic heat shock response (HSR) [17]. Also, the mitochondrial biogenetic pathway relies on nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Mutation of the nDNA and mtDNA produce mitochondrial stress resulting in deregulation of cell signaling and enhanced tumorigenesis, causing impaired respiratory chain function and increased aerobic glycolysis [18, 19].

The quality control, folding process, and import of the mitochondrial proteome and genome are monitored through the UPR^{mt} retrograde transcriptional mechanism. And also, stress like mitochondrial damage, altered mtDNA number, mtDNA mutation, mitochondrial enzyme defects, and mitochondrial dysfunction can cause UPR^{mt}, which will induce tumor progression and tumorigenesis (Fig. 2). The UPR^{mt} is transcribed through the expression of mitochondrial chaperones and proteases as a counteraction towards the misfolded protein within the mitochondrial matrix.

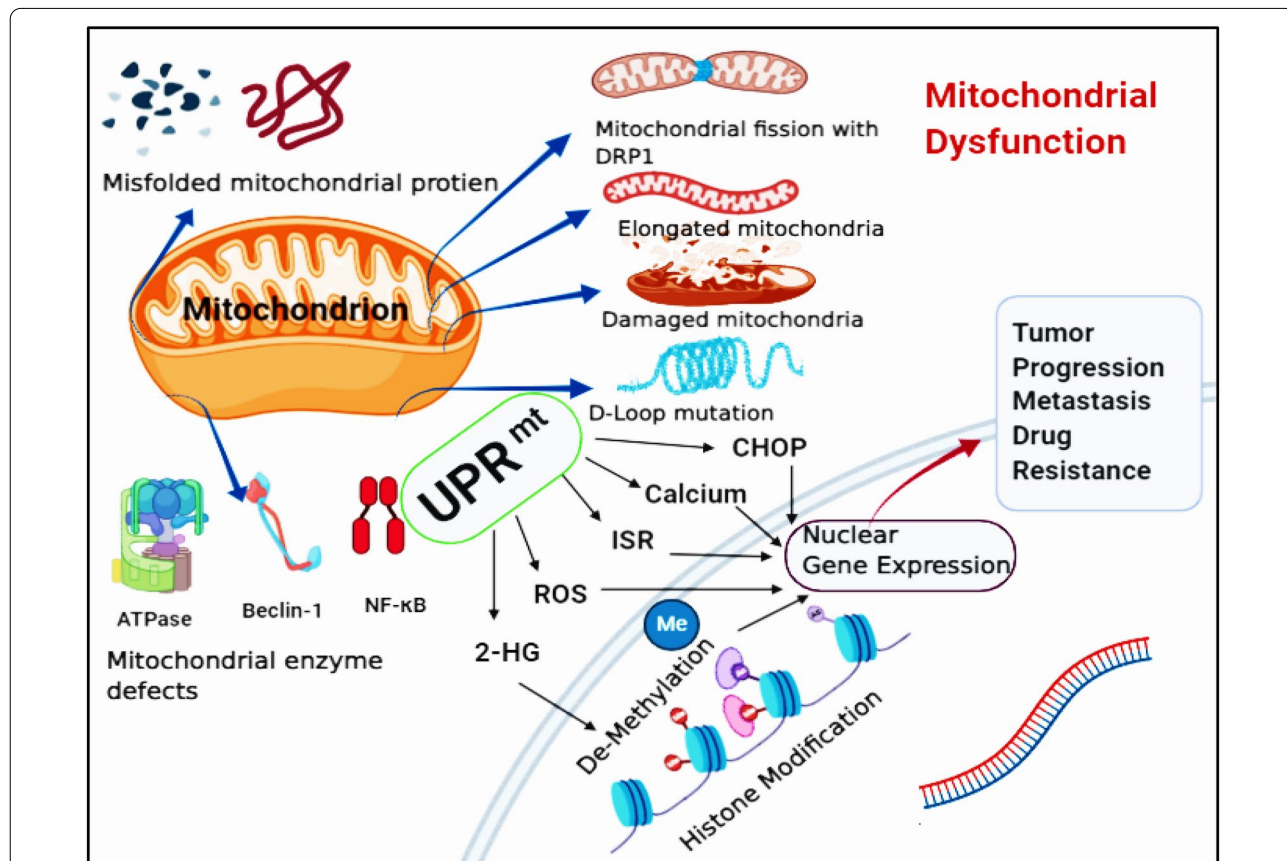


Fig. 2 Synopsis of mitochondrial stress response UPR^{mt} inducing tumor progression and tumorigenesis. Stress like mitochondrial damage, altered mtDNA number, mtDNA mutation, mitochondrial enzyme defects, and mitochondrial dysfunction can cause UPR^{mt} and ISR

Based on the endogenous and exogenous stress conditions, tumor cells produce multiple stress response pathways. The cytosolic heat response pathway is one prominent pathway within the cytosol producing chaperones protein, namely HSP27 and HSP90 engaged in protein folding through heat shock factor regulation [20, 21]. The mtDNA mutation enhances mtDNA's depletion, producing overexpression of the nuclear-encoded chaperones such as HSP10 and HSP60 [22, 23]. Thus mitochondrial misfolding and proliferation of the stress protein and aggregates activate UPR^{mt} in tumor cells [24].

Factors such as aging and hypoxia promote mitochondrial misfolding and aggregation of the stress protein within the mitochondrial matrix. The mtDNA is more prone to depletion and mutation due to lack of histones and reduced DNA repair mechanisms within the mitochondria, and also ROS in tumor cells oxidizes the stress protein causing misfolding [25–27]. Differently from normal cells that depend on oxidative phosphorylation for energy supply, carcinoma cells switch to glycolysis for energy production (Warburg effect), which is a hallmark of tumors. Glycolysis regulating factors, such as hypoxia-inducible factor-1 (HIF-1), phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR), involve the switch of the glycolytic pathway, contributing to cancer proliferation and metastasis [28, 29]. The rapid proliferation of carcinoma cells further worsens the anoxic state and then produces elevated ROS. The prolonged hypoxia induces protein misfolding and accumulation of stress protein, initiating the UPR^{mt} [30, 31]. The import efficacy of activating transcription factors 4 and 5 (ATF 4 and ATF5) is further reduced upon exogenous and endogenous stress [32, 33]. The reduced mitochondrial homeostasis activates the PERK axis of UPR^{mt} and induces the expression of pro-apoptotic protein CHOP, ATF5, and ATF4 [34]. Compared with normal cells, UPR^{mt} exhibit different outcomes in carcinoma cells through multiple signal pathways and effectors, by

which UPR^{mt} promotes cell proliferation and metastasis (Table 1).

In order to mitigate the stress, the retrograde signaling of mitochondria to the nuclear genome is activated. The retrograde pathway relies on ROS, ATP production, transcription regulatory components, essential proteins (histone acetylation) [35, 36]. Transcriptional factors of UPR^{mt} such as AKT, AMPK, CHOP identified stress and increased ROS inside the mitochondrial matrix [37]. In *C. elegans*, during the mitochondrial stress, cytosolic aggregation of ATFS1 encoding both mitochondrial and nuclear signals transcripts UPR^{mt} and OXPHOS genes. The mitochondrial stress recovery is initiated through ATFS-1 action on HSP60, HSP70, and OXPHOS components [38]. In mammalian cells, downregulation of ATF5 retards mitochondrial respiration [33]. And also the proliferation and survival of tumor cells are mediated through gene expression of Egr-1, BCL-2, and MCL1 by ATF-5 [39]. The cell survival and growth of various tumors, namely colorectal, lung tumor, glioma, pancreatic, and breast tumor, are upregulated by ATF5 [40–42]. In addition to the above factors OXPHOS I-V complex impairment also induces UPR^{mt}.

In the case of prolonged endogenous mitochondrial stress, the mitochondrial membrane releases cytochrome C inside the cytosol. The cytochrome C reacts with the apoptotic protease activating factor (Apaf-1) to release caspase 9. Thereby apoptosome initiates caspase-9 to activate further caspase-3 and caspase-7, which produces cellular apoptosis [43]. The tumor cells hold an elevated apoptotic threshold than the normal cells resulting in more tumor cell apoptosis [44]. The energy needed for mitochondrial biogenesis is maintained through sirtuins (Sirt 1–7). Sirt 1 binds with NAD⁺ and deacetylates PGC-1 α and enhances the transcription and translocation of stress genes HSP60, SOD, and ClpP. The antioxidant mechanism of cells is maintained through polyADP-ribose polymerase (PARP) utilizing NAD⁺. Henceforth the inhibition of the PARP inside the

Table 1 Comparison of UPR^{mt} between cancer cells and normal cells

	UPR ^{mt} in cancer cells	UPR ^{mt} in normal cells
Cell type	All type of the carcinoma cells	Post-mitotic cells
Activator	Accumulation unfolded proteins, impaired ETC, mtdna mutation and deletion, inhibition of mitochondrial chaperones or proteases, increased ROS level	Accumulation unfolded proteins, impaired ETC, mtDNA mutation and deletion, inhibition of mitochondrial chaperones or proteases, increased ROS level
Regulatory pathway	CHOP-, SIR3/7-, Pink-, Nrf-, calcium-, and ATF4/5-mediated signal pathway	SIR3/7-, and ATF4/5-mediated signal pathway
Effector	FOXOs, HSPs, HIF, ClpP, SOD1/2, MAPK, OXPHOS-related proteins, proteasome, mitochondrial ribosomal protein	HSPs, SOD1/2, OXPHOS-related proteins, proteasome
Outcome	Cancer proliferation and metastasis	Cell longevity and lifespan extension

mitochondrial matrix enhances the availability of NAD⁺ for Sirt1. Therefore, Sirt1 promotes the activation of the UPR^{mt} [45]. The nuclear respiratory factor (NRF1) binds with Sirt7 and suppresses mitochondrial metabolism. Further, the reduction in Sirt 7 enhances the stress factor, such as HSP60, HSP10, ClpP, and cell proliferation [46].

UPR^{mt} exhibits high potential stress factors in tumor cells, especially the prosurvival effect of the UPR^{mt} protects the cells from the tumor suppression mechanism. The upregulation of the HSP60, HSP10, SIRT3, and hindrance of CHOP pathway due to UPR^{mt} of the tumor cells enhances the chemoresistance, aggressive growth, and hindered biogenetic pathway inside the tumor cells [47, 48]. The external stress such as hypoxia, mitochondrial DNA mutation, environmental stress affects the electron transport chain causing misfolding and denaturing of the proteins, thereby executing the mito-nuclear imbalance which activates the UPR^{mt} which protects the tumor cells from suppression mechanism and apoptosis.

Mitochondrial dysfunction, mitochondrial mutation, UPR^{mt}, and metastatic tumors

Mitochondrial dysfunction enhanced aerobic glycolysis, and impaired mitochondria are predominantly perceived in tumor cells than in normal cells. In human carcinogenic cells, various mtDNA impairments such as mtDNA copy number variations, mitochondrial enzyme defects, a point mutation in the mitochondria, insertion, and large-scale mitochondrial deletion are widely observed [49]. The mtDNA copy number either increased or decreased in numerous carcinoma, namely in hepatic tumors, gastrointestinal cancer, and breast cancers; the mtDNA copy is reduced. In contrast, the mtDNA copy increases in glioma, lymphoma, colorectal carcinoma, and endometrial adenocarcinoma [50–52]. The predominant mutation in mtDNA is found in the D-loop "hot spot" region in the carcinoma cells [53]. Further, the mtDNA mutation is followed in the protein-encoding region, rRNA, and tRNA genes. The mtDNA mutation subsequently resulted in mitophagy, mitochondrial dysfunction, and increased ROS production [54].

The metastatic mtDNA mutation produces metastasis within non-metastatic nuclei due to enhanced ROS production caused by the *ND6* gene (G13997A and 13885insC) mutation. Ishikawa et al. stated that metastasis is induced through upregulation of nuclear-encoded genes such as *HIF-1a*, *MCL-1*, and *VEGF* [55, 56]. The metastatic breast cancer cell line MDA-MB-231 cells with mitochondrial genome showed complex I defect [56]. Various carcinoma cells exhibit large-scale mtDNA deletion, such as 4977 bp, which inhibit the reduction of 5 tRNA genes and 7 protein-encoding genes. NADPH quinone oxidoreductase 1 (NQO1) deficiency enhances

the ROS production in oral and breast cancer due to mtDNA 4977 gene deletion [57–60]. The mtDNA mutations affect the complex I of the electron transport chain in metastatic cancers. The downregulation of *NDUFV1* induces complex I dysfunction, which enhances the metastasis [61].

The mitochondrial genome is highly vulnerable to oxidative defects and ROS production due to OXPHOS impairment due to mutations. The ROS production induces an apoptosis signal in the tumorigenesis pathway [62, 63]. McMahon et al. studied breast cancer from 99 women; around 73.7% of women exhibited somatic mtDNA mutation encoding for complex I [64]. Yuan et al. identified nonsense mtDNA mutation in the *ND6* gene of lung adenocarcinoma, inducing increased ROS production [65]. Carcinogenic cell mutations appear in the mitochondrial enzymes such as fumarate hydratase (FH), succinate dehydrogenase (SDH), and isocitrate dehydrogenase (IDH). The FH mutation of mitochondrial enzyme induces enhanced carcinogenic risk in renal carcinoma and leiomyosarcoma, SDH mutation induces carcinoma in neuroblastoma, and IDH causes malignant cancers like glioma, myeloid neoplasia, chondrosarcoma, and cholangiocarcinoma [66–68]. Mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase, Sirtuin-3 (Sirt 3) defect downregulates mtDNA repair gene (8-oxoguanine DNA glycosylase, *OGG1-2a*), increasing the proliferation of oral cancer, breast cancer, head and neck carcinoma [69, 70].

Mitophagy plays an important role in mitochondrial quality control and cell survival through selective removal of dysfunctional or damaged mitochondria. In normal cells, mitophagy prevents the accumulation of the damaged organelles and inhibits cell carcinogenesis by maintaining a pool of healthy mitochondria. However, mitophagy can provide nutrients for cancer cells by degrading organelles and then promotes tumor growth, since the mitophagy regulators of cancer cells comprise a various of constituents that regulate stress response, cell cycle, survival pathway and ECM detachment during carcinoma proliferation and metastasis, such as AMPK, FOXOs, Sirtuins, ATF4/5 [71]. Therefore, mitophagy can be used as an anticancer target to inhibit cancer cell proliferation.

The endogenous and exogenous stress causes mitochondrial dysfunction, which further exhibit retrograde signalling to regulate the cellular homeostasis and protect the cells through retrograde regulation of genes. The mitochondrial subunits, such as mtDNA, mtRNA, human, and MOTS-c, hold a crucial role in retrograde signalling [72]. The increased ROS production in cancer initiates the retrograde signalling to enhance antioxidant activity through nuclear erythroid related factors 2

(NRF2), enhancing mitochondrial biogenesis through the JNK-PGC1a pathway and increase mitochondrial complex II phosphorylation [73–75]. Also, in tumor cells, the increased ROS enhances tumor progression through nuclear factor- κ B (NF κ B). The mtDNA mutation, mitochondrial dysfunction, and defective OXPHOS can induce Ca⁺ release from mitochondria. The cytosolic calcium in the mitochondria induces calcium retrograde signaling via activation of NF- κ B, Jun-N-terminal kinase (JNK) and p38 MAPK pathway, upregulation of CREB, early growth response protein 1 (EGR1), ATF2, CCAAT/enhancer-binding protein-d and CHOP [76, 77]. Thus ROS and Ca²⁺ play a crucial role in the mitochondrial mechanism.

In UPR^{mt}, the upregulated mitochondrial misfolded ornithine transcarbamylase (OTCA) activates the transcription of CHOP, proteases, ClpP, and chaperones HSP60, HSP70 due to the proteomic mitochondrial stress. The OMI/HTRA2, NRF1, and proteasome transcription are activated through the estrogen receptor alpha (Er α) of the UPR^{mt} axis, and the SIRT3 UPR^{mt} axis induces antioxidant genes and helps in the removal of damaged mitochondria through mitophagy [78, 79]. In ISR, electron transport chain (ETC) dysfunction, increased ROS, and UPR^{mt} induce GCN2, PERK, and HRI based on the stress of the tumor environment. In UPR^{mt}, integrated stress response (ISR) plays a key role in adaptation to stress. The ISR acts based on eukaryotic translation initiation factor 2 α kinases (eIF2 α) accountable for cap-dependent protein translation and activation

transcription factor-4 (ATF-4) [80]. The eIF2 α - ATF-4 pathway is more prominent in the tumor cells. The down-regulation of ATF4 decreases the carcinoma, whereas the upregulation of ATF4 promotes tumor progression through GCN2 activation [81, 82]. The UPR^{mt} axis, including SIRT3, PERK, CHOP, ATF4/5, ETC pathways, mainly aggravates the tumor progression (Fig. 3, Table 2).

Upregulation of HSP60 and ATF5 during UPR^{mt} predominantly increases the carcinoma cell's survival threshold and promotes tumor progression, therapeutic resistance, and resistance towards apoptosis [39, 83]. Inhibition of ATF5 enhances the growth of human glioblastoma cells and human pancreatic cancer cells [84]. The UPR^{mt} relies on SIRT3 for deacetylation and further relocalization of FOXO3a to the nucleus and SOD2 for the antioxidant response. The significant increase in SIRT3/FOXO3a/SOD2 UPR^{mt} axis demonstrated a high risk of tumor progression in head and neck cancer [85]. UPR^{mt} in acute myeloid leukemia showed increased cell apoptosis due to BCL2 inhibition caused by knockdown of SDHB, thereby affecting the respiratory chain complex II [86]. In ROS production and UPR^{mt} superoxide dismutase, SOD1 and SOD2 play a vital role. On UPR^{mt} activation, the intermembrane space (IMS) found SOD1 found to be increased than SOD2 in breast carcinoma cells [10, 87].

The UPR^{mt} activation of breast cancer exhibits depletion of mitochondrial metalloproteinase OMA1, causing mitochondrial homeostasis and increased ki67 expression genes promoting metastatic growth of cancer [88].

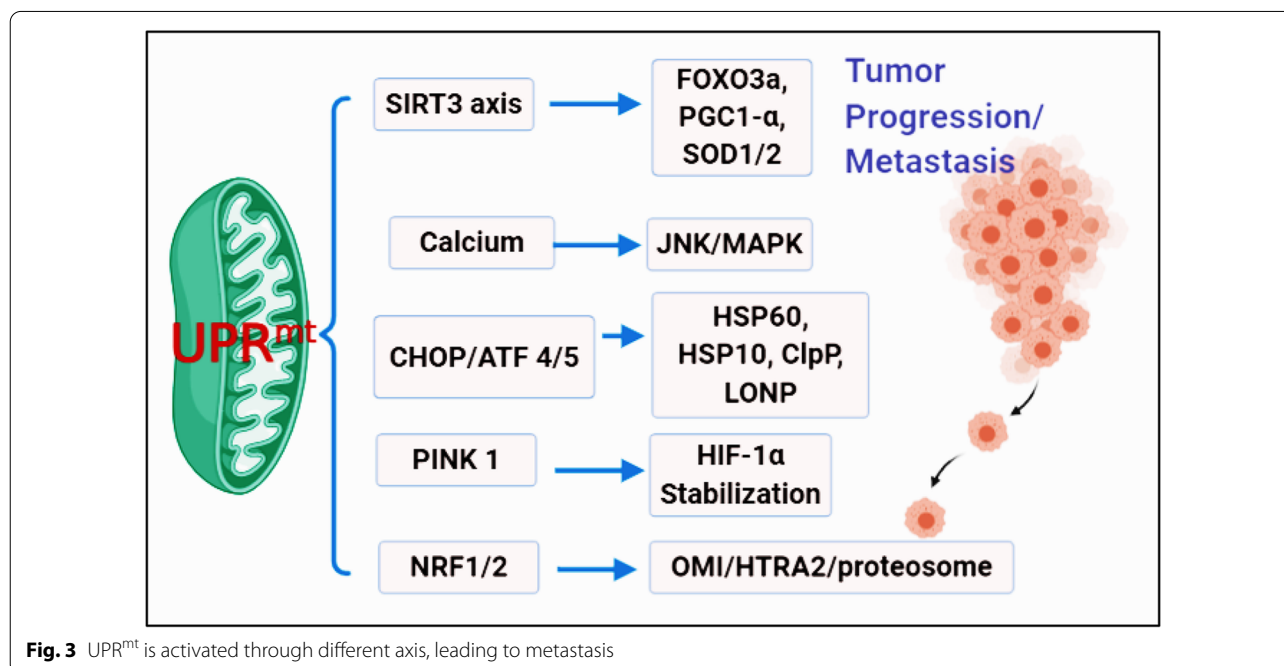


Fig. 3 UPR^{mt} is activated through different axis, leading to metastasis

The inhibition of ClpP exhibit the anti-tumor effect in both in vitro and in vivo conditions in the leukemia cells. The upregulation of ClpP is prominently found in metastatic tumors [89, 90]. In UPR^{mt} activated breast carcinoma cells, overexpression of Her-2 is observed by Chen et al. [91]. The UPR^{mt} exhibits initiation of c-jun through binding of JNK2 to increase CHOP and C/EBP β , which increase HSP60 and HSP10 in breast cancer [34]. Further mtDNA mutation targeting ND3 (A10398G) in bone carcinoma cells colonizes bone carcinoma cells [92]. The breast carcinoma cells contain low SIRT3 than the normal MCF10A cells due to UPR^{mt}. SIRT3 and SOD2 are decreased in the breast carcinoma cells with activated UPR^{mt} [93]. Hu et al. stated that the carcinoma cells upregulate genome BNIP3, a mitophagy enhancing agent, to adapt to hypoxia produced during antiangiogenic therapeutics [94]. The enhanced ROS level in the carcinoma cell promotes increased metastasis and invasiveness due to enhanced UPR^{mt} to maintain cell toxicity and cell viability [95].

Further, Lin et al. observed elevated fascin level through the enhanced oxidative mechanism in lung carcinoma cells in the metastatic stages due to mitochondrial F-actin's stability [96]. The knockdown of BRCA1 or BRCA2 gene expression in breast carcinoma cells increases hydrogen peroxide formation in carcinoma cells and neighboring stroma cells [97, 98]. The knockdown of BNIP3 expression is prominently found in pancreatic and breast cancer progression [99–102]. Upregulation of carbonic anhydrase IX (CAIX) is induced through UPR^{mt} through transcription of HIF-1 α , thereby increasing high-risk carcinoma proliferation, metastasis, and locoregional failure [103, 104]. The upregulation of SIRT3 due to UPR^{mt} elevates the ROS production and stabilization of HIF-1 α , which initiates the switching of the anaerobic glycolytic process, the Warburg effect in various carcinomas, including breast cancer, hepatic, gastric, and colorectal carcinoma [105].

The switching of the anaerobic glycolytic process retard/delete the Parkin or Pink1, thereby increasing ROS and HIF-1 α deletion, enhancing tumorigenesis and proliferation of kras-mutant pancreatic ductal adenocarcinoma (PDAC) [106]. NIX (BNIP3L) expression is responsive for UPR^{mt}, and it downregulates sphingosine kinase 1 (SPHK1) localized in mitochondria [107, 108]. The glycolytic process increases the mitochondrial Ca²⁺ through mitochondrial calcium uniporter (MCU), thus overexpressed MCU channels are widely found in breast carcinoma patients [109, 110]. The pyruvate dehydrogenase kinase 1 (PDK1) controls the mitochondrial quality and plays a crucial role in the TAC cycle and OXPHOS I-V complex. The downregulation of PDK1 initiates mitochondrial quality disorders and increases metastasis

[111]. Sun et al. observed increased mitochondrial fission and upregulation of Drp1 expression in the hepatocellular carcinoma cells, and further, it promotes proliferation and metastasis [112].

In various types of carcinomas, overexpression of mitochondrial ribosomal protein (MRPs) such as MRPL38, MRPS27, and MRPL10 are widely observed due to transcription of UPR^{mt} [113]. The knockdown of SIRT3 expression in tumor growth increases ROS production and focal adhesion kinase (FAK) activation [114]. Mitochondrial transcriptional factor A (TFAM) mediate and regulate the mtDNA copy number, defective mitochondria, damaged molecular pattern, inflammation. TFAM initiates the mtDNA copy number through enhanced OXPHOS in colorectal carcinoma. Further, TFAM affects the calcium transport, flagella associated protein 65(CFAP65) synthesis, and cytoplasmic phosphoenolpyruvate carboxykinase (PCK1) expression through retrograde mitochondrial signaling and UPR^{mt} activation, which further increases carcinoma proliferation and progression [115, 116]. Mitohormesis is observed due to UPR^{mt} activation, which produces carcinoma invasion, multiplication, and metastasis in various cancers [95]. FH and SDH mutations initiate retrograde mitochondrial signaling, leading to the accumulation of fumarate and succinate in the carcinoma cells due to UPR^{mt}. Further accumulation of fumarate, succinate, 2-HG (D-2-hydroxyglutaric acid) enhances malignancies. And also, 2-HG affects the metabolism of complex IV/V resulting in deregulation of the mitochondrial energetics, stabilization of HIF-1 α , and carcinoma progression. Further 2-HG accumulation produces mtDNA de-methylation causing genetic mutation in the carcinoma cells [117–119]. The retrograde signaling initiates the loss of heterozygosity (LOH) observed in the carcinoma patients' leiomyomatosis and renal carcinomas due to germline FH mutations [120]. The mitochondrial dysfunction and retrograde mitochondrial signaling evidentially produced overexpression of fibroblast growth factor 21 (fgf21) and growth differentiation factor 15 (gdf15) in tumor patients [121, 122].

The UPR^{mt} through exogenous and endogenous stress alters the epigenome through substantial chromatin reorientation initiated through histone, namely, methyltransferase MET 2 and nuclear cofactor LIN65, exhibiting switching in the pattern of H3K9me methylation. During mitochondrial dysfunction initiated chromatin alteration and downregulation of the UPR^{mt} genes, the transcriptional regulators ATFS 1 and DVE 1 initiates proteostasis and cell longevity [123, 124]. The further studies on UPR^{mt} explained that the transcriptional genes activating UPR^{mt} contain two supplementary elements on both sides of the CHOP/CEBP β component

called mitochondrial response elements (MURE 1 & 2) [125]. The minor missense mutation of the mitochondrial genome in the non-protein region promotes metastasis in the carcinoma cells [126]. The mutated mitochondrial DNA further affects and retard the mtDNA copy number due to activated UPR^{mt}, further enhancing mitochondrial biogenesis and mtDNA replication [127]. The studies revealed mtDNA alterations and mtDNA mutations play a crucial role in the activation of UPR^{mt}, which in turn increases mitochondrial health, which further positively influences the proliferation and metastasis in the carcinoma [128]. The synopsis of the mitochondrial dysfunction, UPR^{mt} metabolism, and pathway are precisely tabulated as follows (Table 1).

Tumor theranostics and UPR^{mt}

Mitochondria-nuclear retrograde pathway (mito-nuclear pathway) is a signal communication from mitochondria to nucleus. Mito-nuclear pathway employs various retrograde signals to regulate nuclear gene expression to maintain cell homeostasis. UPR^{mt} is an important

pathway in the retrograde mito-nuclear communication widely observed in carcinoma cells. The activated UPR^{mt} pathway can induce nuclear gene to express various proteins to stabilize the structure of dysfunctional mitochondria of carcinoma cells, which will continue to provide metabolic intermediates for maintaining the cell proliferation. Henceforth UPR^{mt} can be utilized as a specific target for drugs to inhibit tumor growth (Fig. 4). Selective drugs target the inhibition of proteases, and chaperones should be synthesized to produce almost 100% efficacy in the treatment of carcinoma. The anti-tumor drugs such as Bortezomib and nelfinavir, which are proteasome inhibitors, are utilized to hinder the UPR pathway through downregulation of VEGF factor to retard the tumor vasculature [129–134]. Geldanamycin inhibits the UPR pathway’s chaperones, reduces the HIF1-α stabilization, and stimulates the hypoxic carcinoma death [135]. The tumor theranostic utilizing Gamitrinib enhanced specific tumor apoptosis through inhibiting TNF receptor-associated protein-1 (TRAP-1) chaperones [136, 137]. The therapeutic anti-cancer agent LCS-1

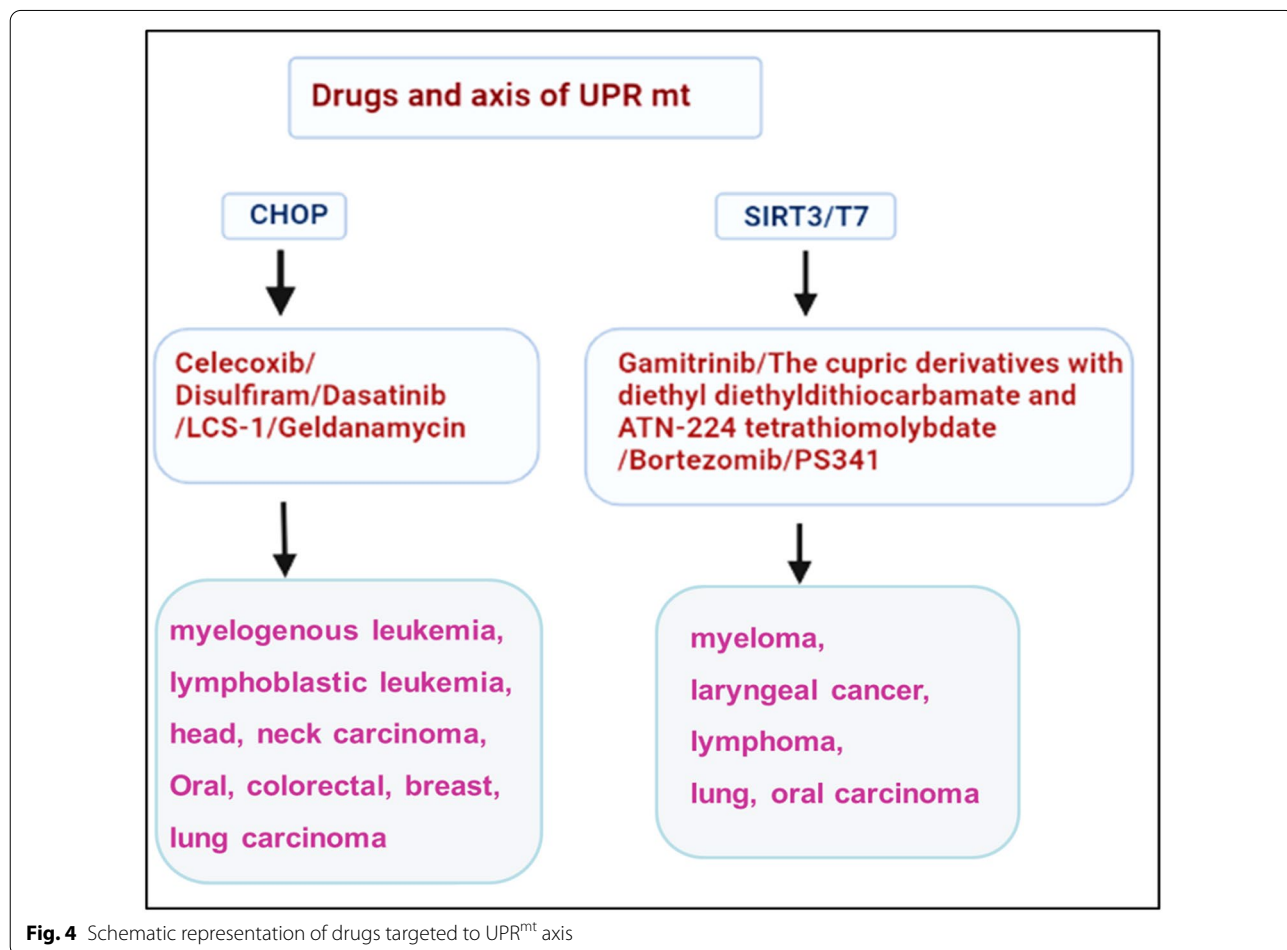


Fig. 4 Schematic representation of drugs targeted to UPR^{mt} axis

Table 2 Mitochondrial dysfunction and pathway of UPR^{mt} in carcinoma cells

Carcinoma cells	Mechanism of UPR ^{mt} activation	Type of axis of activation	References
Lung, breast, glioma cells	HSP60, HSP10 stress protein	CHOP	[23, 24]
Glioblastoma, melanoma, prostate carcinoma cells	Gene expression of Egr-1, BCL-2, and MCL1	CHOP/ATF	[39]
Lung, Pancreatic, Breast, Glioma	ATF-5	CHOP	[40–42]
Breast cancer	PARP inhibition, NRF1 with SIRT7	CHOP/SIRT3	[45, 46]
Hepatic, gastrointestinal, breast carcinoma	Alteration in the mtDNA copy	CHOP/SIRT3/PINK	[49–52]
Breast Carcinoma	ROS production through ND6 gene mutation, upregulation of VEGF	PINK/JNK/HIF- α stabilization	[55]
Breast cancer	Defect in mitochondrial gene complex I	SIRT3/CHOP	[56]
Oral, breast cancer	NQO1 deficiency, 4977 gene deletion	SOD/NRF1	[57–60]
Metastatic cells	Downregulation of NDUFV1	NRF1	[61]
Breast cancer	mtDNA mutation	CHOP/SOD/NRF1	[64]
Lung adenocarcinoma	mtDNA ND6 gene mutation	CHOP/SOD/NRF1	[65]
Renal, neuroblastoma, glioma	FH, SDH, IDH enzyme mutation	CHOP/NRF1	[66–68]
Head, neck, oral, breast	Downregulation of OGG1-2a	SIRT3	[69, 70]
Breast, Renal and Pancreatic carcinoma	PINK1/BCI-2, BNIP3/NIX overexpression	SIRT3/CHOP/NRF1	[71]
Hepatocellular carcinoma cells	ROS production	NRF2/PGC 1 α /JNK	[73–75]
Fibrosarcoma (mesenchymal tumor)	Calcium dysfunction, Inhibition of NF- κ B, Ros production	CHOP/EGR1/JNK/MAPK	[76, 77]
Breast carcinoma cells	OMI/HTRA2, NRF1	SIRT3	[78, 79]
Fibrosarcoma, colorectal adenocarcinoma	Knockdown of ATF4, ATF4 expression inhibition through GCN2 activation	CHOP/SIRT3	[81, 82]
Glioblastoma, pancreatic cancer	Inhibition of ATF5	CHOP	[84]
Head, neck cancer	SIRT3/FOXO3a/SOD2	CHOP/SIRT3	[85]
Myeloid leukemia	Inhibition of Bcl2, knockdown of SDHB	NFR1/2	[86]
Breast cancer	ROS production	NFR1/2/CHOP	[10, 87]
Breast cancer	Depletion of OMA1 increased gene expression ki67	CHOP/NFR1/PINK	[88]
Myeloid leukemia metastatic cancer	Inhibition of ClpP	CHOP	[89, 90]
Breast cancer	Overexpression of Her2	CHOP	[91]
Breast cancer	Inhibition of JNK2	CHOP	[34]
Bone carcinoma	ND3 mutation	CHOP/SIRT3	[92]
Breast carcinoma	ROS production, SOD1/2	SIRT3	[93]
Glioblastoma	BNIP3 upregulation	CHOP/SIRT3/NFR1/2	[94]
Lung carcinoma	Elevated fascin	CHOP	[96]
Breast	Knockdown of BRCA1/2	SOD/NFR1	[97, 98]
Glioblastoma	Downregulation of PINK, HIF-1 α stabilization	CHOP/PINK/NRF	[99]
Breast, pancreatic cancer	Knockdown of BNIP3	CHOP/NRF1/SOD	[100–102]
Breast, neck, colorectal, head carcinoma	Upregulation CAIX, HIF 1- α stabilization	CHOP/SIRT3	[103, 104]
Gastric, breast, colorectal carcinoma	ROS production, HIF 1- α stabilization	SIRT3	[105]
Pancreatic ductal adenocarcinoma	ROS production, HIF 1- α deletion	PINK1/Parkin	[106]
Ovarian, lung, colorectal carcinoma cells	BNIP3/NIX downregulates SPHK1	CHOP/SIRT3	[107, 108]
Breast cancer	Overexpression of MCU	Calcium/CHOP	[109, 110]
Liver cancer lining	Knockdown of PDK1	CHOP/NRF1/2	[111]
Hepatocellular carcinoma	Upregulation of DRp1, mitochondrial fission	CHOP/NRF1	[112]
Renal carcinoma cells	2-HG, de-methylation of histone	CHOP/PINK	[117–119]
Renal and colorectal carcinoma cells	Overexpression of FGF21, GDF15	CHOP/NFR1	[121, 122]

inhibited the progression of lung carcinoma cell, neck, head carcinoma [138, 139]. The cupric derivatives with diethyl diethyldithiocarbamate and ATN-224 tetrathiomolybdate inhibited the SOD1 pathway of the tumor progression and thereby exhibited apoptosis of lung carcinoma [140, 141]. The carcinoma prodrug of glutamine antagonist 6-diazo-5-oxo-L-norleucine (DON) improved the T cell mitochondrial metabolism in the tumor cells to enhance the efficacy of the anti-tumor effect [142]. Bortezomib/PS341 is one of the potential di-peptidyl boronic acid components utilized as the 26S proteasome inhibition in treating myeloma, laryngeal cancer, and lymphoma [143]. Moreover, the drugs that target UPR^{mt} include Carfilzomib and Oprozomib, which are widely utilized in oral, HNSCC, and multiple myeloma in cancer therapy by inhibiting MCL-1 [144]. The UPR^{mt} activation of disulfiram induces apoptosis in oral and pharyngeal tumor cells via CHOP [145]. Celecoxib drug studies illustrated the ant-cancer activity and induced apoptosis in oral, head, neck, colorectal carcinoma via CHOP and BNIP3 pathway [146]. The pyrimidine and thiazole based drug dasatinib studies revealed effective anti-cancer activity in myelogenous leukemia, lymphoblastic leukemia, head and neck carcinoma. Dasatinib inhibits cancers via knockdown of AMPK and CHOP pathways of carcinoma. Dasatinib is a multikinase inhibitor that has been approved by FDA for treating chronic myelogenous leukemia. Nevertheless, the anticancer mechanism of dasatinib is more complex than expected. For example, AMPK-dependent stress is proved to involve the dasatinib-induced apoptosis [147]. In addition, the inhibition effect of dasatinib on gastric cancer is reported that is mediated by CHOP [148].

Moreover, mitochondrial therapy (mitotherapy) are found to be one efficient methodology to treat carcinoma cells. Mitotherapy is to transfer the isolated healthy mitochondria into cultured cells by incubation and into animals by injection, then the exogenous mitochondria

will play roles in cells. Recent studies have shown that the mitotherapy can inhibit rapid proliferation of tumors, including breast cancer, glioma, and melanoma. Studies have revealed that mitotherapy can inhibit tumor cell glycolysis, and reduce ATP and lactate production after the healthy mitochondria enter cancer cells. In addition, healthy mitochondria can reduce oxidative damage, thereby retards UPR^{mt} and cancer proliferation [149–152]. In addition, efficient anti-cancer drug and cancer apoptosis can be achieved through targeting the mitochondrial stress response components like ClpP, proteases, and chaperones [89, 153–157]. The various FDA approved UPR^{mt} components, chaperones, and proteasome inhibitor drugs of carcinoma are listed below in Table 3.

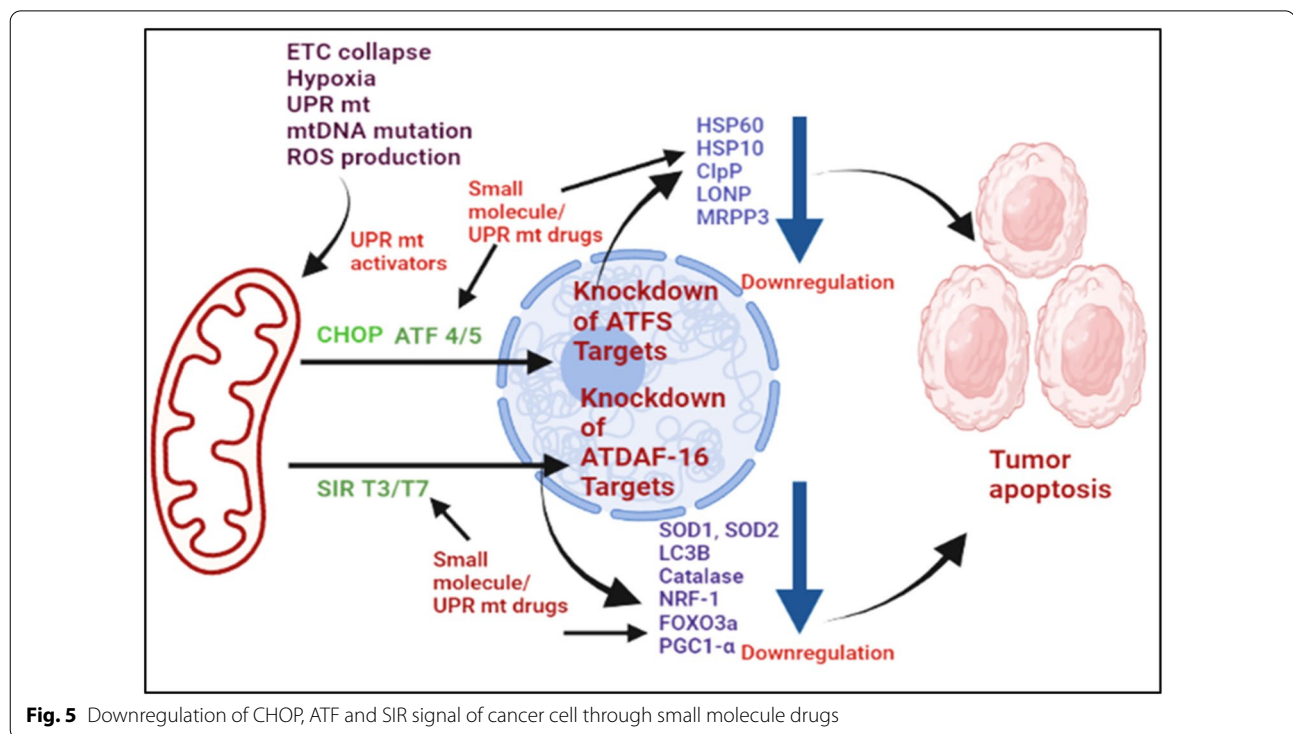
Conclusion

The oncology and tumor therapeutic field in realizing that mitochondrial metabolism plays a crucial role in modeling the futuristic drug would achieve great progress. Mitochondrial dysfunction, including change in mtDNA copy number, mtDNA mutation, mitochondrial enzyme defects activate the UPR^{mt} retrograde signal from mitochondria to nucleus, then nuclear genes express mitochondria-related proteins to protect the dysfunctional mitochondria, and meanwhile to facilitate the dysfunctional mitochondria to provide energy and intermediate metabolites for tumor proliferation and metastasis. The critical importance of cancer modeling therapeutic should target the UPR^{mt} through small molecule drug therapy and mitotherapy.

On the basis of understanding the molecular mechanism of UPR^{mt}, targeted downregulation of UPR^{mt} signal molecules, including CHOP, ATF-5, and SIRT3, would retard tumor growth and induce the cell apoptosis (Fig. 5). And also, drugs that target the CHOP/SIRT3/NRF1/2 signal pathway should achieve maximum tumor death or eradication efficacy. Therefore,

Table 3 Drugs inhibiting UPR^{mt}-mediated chaperones and proteases pathway in carcinoma cells

Drug	Carcinoma type	Inhibition pathway	References
Geldanamycin	Metastatic cells, breast, lung carcinoma	Inhibition of CHOP/HIF-1 α	[135]
Gamitrinib	Oral, breast, hepatocellular	Inhibiting sirt3/7-tnf receptor-associated protein-1 (trap-1)	[136, 137]
LCS-1	Lung carcinoma cell, neck, head carcinoma	Inhibition of chop	[138, 139]
The cupric derivatives with diethyl diethyldithiocarbamate and ATN-224 tetrathiomolybdate	Lung carcinoma cell	Inhibited the sirt7/sod1 pathway	[140, 141]
Bortezomib/PS341	Myeloma, laryngeal cancer, and lymphoma	Inhibition of sirt7/26 s proteasome	[143]
Disulfiram	Oral and pharyngeal tumor cells	CHOP	[145]
Celecoxib	Oral, head, neck, colorectal carcinoma	CHOP/BNIP3	[146]
Dasatinib	Myelogenous leukemia, lymphoblastic leukemia, head and neck carcinoma	Inhibition of CHOP and AMPK pathway	[147, 148]



the exploitation of targeted drugs for blocking UPR^{mt} is a prominent strategy to treat metastasis tumors through a sustainable mechanism in tumor therapy.

Abbreviations

AKT: Serine/threonine-protein kinase; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; Apaf-1: Apoptotic protease activating factor; ATF: Activating transcription factor; BNIP3: BCL-2/adenovirus E1B protein-binding protein 3; CFAP65: Cilia and flagella associated protein 65; CHOP: C/EBP homologous protein; ClpP: Caseinolytic peptidase; CREB: CAMP-response element binding protein; DON: 6-Diazo-5-oxo-L-norleucine; EGR: Early growth response protein; EGR1: Early growth response protein 1; eIF2α: Elongation Initiation factor 2α kinases; Era: Estrogen receptor alpha; ETC: Electron transport chain; FAK: Focal adhesion kinase; fgf21: Fibroblast growth factor 21; FH: Fumarate hydratase; gdf15: Growth differentiation factor 15; HIF: Hypoxia-inducible factor; HSF: Heat shock transcription factor; HSP: Heat shock protein; HSR: Cytosolic heat shock response; IDH: Isocitrate dehydrogenase; ISR: Integrated stress response; JNK: Jun-N-terminal kinase; LONP: Lon protease; MCU: Mitochondrial calcium uniporter; MRP: Mitochondrial ribosomal protein; mtDNA: Mitochondrial DNA; NADH: Nicotinamide adenine dinucleotide; NADPH: Nicotinamide adenine dinucleotide phosphate; NQO1: Quinone oxidoreductase 1; NRF: Nuclear respiratory factor; NRF2: Nuclear erythroid related factors 2; OGG1-2a: 8-Oxoguanine DNA glycosylase; OXPHOS: Oxidative phosphorylation disorder; PARP: PolyADP-ribose polymerase; PCK: Cytoplasmic phosphoenolpyruvate carboxykinase; PDK: Pyruvate dehydrogenase kinase; PINK1: PTEN-induced putative kinase 1; PQC: Protein quality control; ROS: Reactive oxygen species; SDH: Succinate dehydrogenase; SIRT: Sirtuin; SOD: Superoxide dismutase; TAC: Tricarboxylic acid cycle; TRAP-1: TNF receptor-associated protein-1; UPR^{mt}: Mitochondrial unfolded protein response.

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Authors' contributions

KR wrote the draft. PD and AF discussed and revised the manuscript. All authors read and approved the final manuscript.

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Declarations

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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