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REVIEW

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Mitochondrial adaptation in cancer drug resistance: prevalence, mechanisms, and management

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Abstract

Drug resistance represents a major obstacle in cancer management, and the mechanisms underlying stress adaptation of cancer cells in response to therapy-induced hostile environment are largely unknown. As the central organelle for cellular energy supply, mitochondria can rapidly undergo dynamic changes and integrate cellular signaling pathways to provide bioenergetic and biosynthetic flexibility for cancer cells, which contributes to multiple aspects of tumor characteristics, including drug resistance. Therefore, targeting mitochondria for cancer therapy and overcoming drug resistance has attracted increasing attention for various types of cancer. Multiple mitochondrial adaptation processes, including mitochondrial dynamics, mitochondrial metabolism, and mitochondrial apoptotic regulatory machinery, have been demonstrated to be potential targets. However, recent increasing insights into mitochondria have revealed the complexity of mitochondrial structure and functions, the elusive functions of mitochondria in tumor biology, and the targeting inaccessibility of mitochondria, which have posed challenges for the clinical application of mitochondrial-based cancer therapeutic strategies. Therefore, discovery of both novel mitochondria-targeting agents and innovative mitochondria-targeting approaches is urgently required. Here, we review the most recent literature to summarize the molecular mechanisms underlying mitochondrial stress adaptation and their intricate connection with cancer drug resistance. In addition, an overview of the emerging strategies to target mitochondria for effectively overcoming chemoresistance is highlighted, with an emphasis on drug repositioning and mitochondrial drug delivery approaches, which may accelerate the application of mitochondria-targeting compounds for cancer therapy.

Keywords: Cancer drug resistance, Mitochondrial dynamics, Mitochondrial adaptation, Drug repurposing, Mitochondrial-targeted drug delivery, Mitochondrial transplantation

Background

Chemotherapy and targeted therapy are mainstream cancer treatments, but their efficiency is limited by frequent drug resistance and tumor relapse [1–3]. Generally, cancer drug resistance can result from two types of mechanism: intrinsic or acquired causes [4–8]. Intrinsic resistance is due to preexisting resistance-mediating factors prior to any treatment administered, while acquired drug resistance is caused by adaptive responses that confer cancer cell survival in unfavorable environments during drug treatment [9–12]. These adaptive

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response mechanisms include reduced uptake of drugs or increased drug efflux, ineffective induction of cell death, and compensatory activation of pro-survival signaling pathways [13–15]. Moreover, it is increasingly recognized that drug resistance can generally arise from a minor resistant subpopulation of cancer cells due to the high incidence of tumor heterogeneity. Recent studies have demonstrated that cancer stem cells (CSCs) are prone to maintain a quiescent state to evade the drug cytotoxicity which contributes to the development of a whole resistance phenotype [16–19]

Cancer cells often reprogram their metabolic pathways to provide energetic and biosynthetic flexibility to survive in hostile conditions when exposed to cancer treatments [20–26]. Metabolic reprogramming is considered as one of the major hallmarks of cancer [27] and has been an area of accelerated research over the last century on the basis of aerobic glycolysis theory proposed by Otto von Warburg, which describes the preference for glycolysis by tumors in the presence of oxygen [28–37]. While numerous studies have well documented the crucial role of metabolic adaptations in supporting cancer progression under endogenous stress such as hypoxia, cancer cells also develop metabolic flexibility to survive in response to exogenous stress including drug administration [28, 38–40]. Chemoresistance caused by glucose metabolic plasticity, for example, is generally mediated by several key glycolytic factors, such as Hexokinase 2 (HK2), glucose transporter 1 (GLUT1), as well as pyruvate kinase isozymes M2 (PKM2) [41–44]. The augmentation of glycolysis results in enhanced secretion of lactate and production of glycolytic intermediates, which activate branching pathways (e.g., pentose phosphate pathway (PPP)) and the stress response machinery to support nucleotide synthesis and redox homeostasis, leading to escape from apoptosis and reduction in drug entry [45, 46]. Correspondingly, targeting the dynamic adaptability of metabolism has obtained considerable effect in improving the efficiency of cancer therapy [47–50].

Mitochondria are the major organelles that provide bioenergetic and biosynthetic changes, which accompany tumor progression by taking up substrates from the cytoplasm to drive the electron transport chain (ETC) and respiration, the tricarboxylic acid cycle (TCA cycle), fatty acid oxidation (FAO), and subsequent macromolecule synthesis (Fig. 1) [51–54]. Additionally, mitochondria can rapidly sense and adapt to stress stimulation to ensure cell survival. Advanced studies on cancer metabolism have expanded our understanding of mitochondrial metabolic alterations to support anabolic requirements of cancer cells, which depend largely on the strictly intertwined plasticity of mitochondria (mitochondrial dynamics), including fusion/fission, trafficking/transfer, and inter-organelle communication/retrograde signaling [55]. While participating in the maintenance of cellular homeostasis during tumor progression, these mitochondrial adaptive processes are also pivotal for handling drug-induced stress, which contributes to alterations in mitochondrial metabolism and subsequent drug resistance [56–59]. For example, mitochondrial fission provides an advantage for cisplatin-resistant cells compared with their nonresistant counterpart under hypoxic conditions in ovarian cancer [60, 61]. In melanoma, the increased oxidative phosphorylation (OXPHOS) in resistant subclones is supported by peroxisome proliferator-activated receptorycoactivator-1 (PGC-1α) and is required for buffering oxidative stress [46]. Indeed, mitochondria have received increasing attention as a therapeutic target for cancer therapy, and several agents targeting mitochondrial metabolism are under investigation [62–64]. However, the dynamic alterations and inaccessible characteristics of mitochondria make it a priority to explore novel mitochondria-targeting agents and strategies.

Here, we address the most recent findings regarding mitochondrial dynamics to indicate their functions in cancer drug resistance. An overview of existing mitochondrial agents will be presented, and emerging strategies for effective tumor elimination by targeting mitochondria, including drug repurposing and mitochondrial-targeted drug delivery systems, will be summarized.

Mitochondrial structure and functions

Mitochondria are one of the most evolutionary conserved intracellular organelles that consist of the outer mitochondrial membrane (OMM) and a highly folded inner mitochondrial membrane (IMM) [65]. These two membranes are separated by the mitochondrial intermembrane space (IMS) and differ from each other in lipid composition and permeability. Importantly, the IMM invaginates into the mitochondrial matrix to form cristae, the crucial structure for mitochondrial function [66]. To maintain these structures, mitochondria undergo multiple complex processes (including fission and fusion) to dynamically control the function of mitochondria under various stimuli [67].

The primary function of mitochondria is demonstrated as energy supply. During the process of energy production, mitochondria integrate several metabolic pathways, including TCA cycle, FAO, amino acid oxidation, OXPHOS, etc., to provide not only most of the cellular ATP but also intermediate metabolite, supporting multiple physiological functions of the organism [68]. In recent decades, numerous studies have demonstrated that mitochondria also function as a signaling organelle to participate in many physiological processes, such as

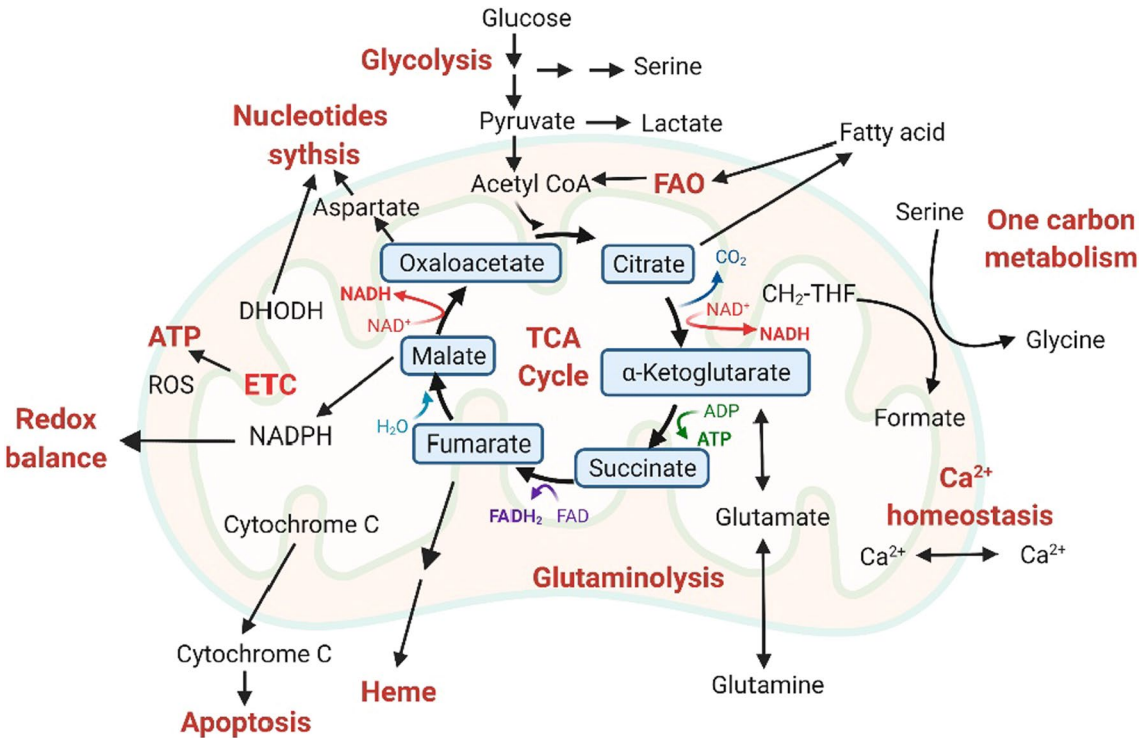

Fig. 1 Mitochondria are energetic and biosynthetic signaling hubs. Mitochondria take up substrates from the cytoplasm to provide bioenergetic and biosynthetic flexibility. The TCA cycle coordinates glycolysis and glutaminolysis to provide blocks necessary for macromolecule (nucleotides, lipids, and amino acids) synthesis. This process produces ATP, NADPH, as well as the electron donors in OXPHOS (NADH and FADH2). The ETC complexes produce the majority of cellular ATP and oxidize NADH and FADH2 to NAD^+ and FAD, respectively, to allow the oxidative TCA cycle to continuously function, producing metabolites that support macromolecule synthesis. DHODH couples de novo pyrimidine synthesis to donate electrons to mitochondrial ubiquinone (CoQ) during the conversion of dihydroorotate to orotate. Mitochondrial dynamics facilitate maximum survival advantages of cancer cells in response to stress by maintaining mitochondrial metabolism, ion homeostasis such as Ca^{2+} signaling, and redox balance

Ca^{2+} homeostasis, redox homeostasis, apoptosis regulation, and synthesis of heme and iron–sulfur clusters [69]. Indeed, mitochondria regulate Ca^{2+} homeostasis by exporting Ca^{2+} absorbed from intracellular store or extracellular uptake, which release Ca^{2+} back to the cytosol for regulation of calcium-dependent signaling [70]. In addition, the by-products of electron transfer during mitochondrial respiration result in the generation of reactive oxygen species (ROS), in which complexes I and III play the central role [71]. These physiological ROS together with the reducing equivalents (NADPH, etc.) generated by mitochondrial metabolism maintain the redox homeostasis for normal biological functions [72]. Moreover, mitochondria are tightly associated with apoptosis induction, as the release of cytochrome c, the key event of intrinsic apoptotic pathway, is mediated by the mitochondrial outer membrane permeabilization (MOMP) [73]. Therefore, the above complicated functions of mitochondria require the sophisticated regulation of mitochondrial dynamics for maintaining normal physiological functions of the organism.

Mitochondrial defects caused by various stimuli may lead to various pathologies, including neurodegenerative diseases, aging, and especially cancer. A large number of studies have suggested that mitochondria dysfunction may promote cancer onset and progression mainly through the following crucial mechanisms. First, as mitochondria are the major source of intracellular ROS, adequate levels of reactive species not only enable the accumulation of oncogenic defects of genes but also favor the activation of several oncogenic signaling pathways, which result in aberrant cell proliferation [74]. In addition, metabolic pathways in mitochondria may lead to the abnormal accumulation of specific metabolites, such as α-ketoglutarate (α-KG), pyruvate, fumarate, and succinate, which display significant oncogenic role during cancer initiation and progression [75–78]. Moreover, alterations or functional defects in MOMP are beneficial for survival of tumor cells when facing harsh conditions (such as hypoxic stress, metabolic stress, and therapeutic stress), thereby resisting regulated cell death [79]. During the dissemination and colonization, mitochondria endow

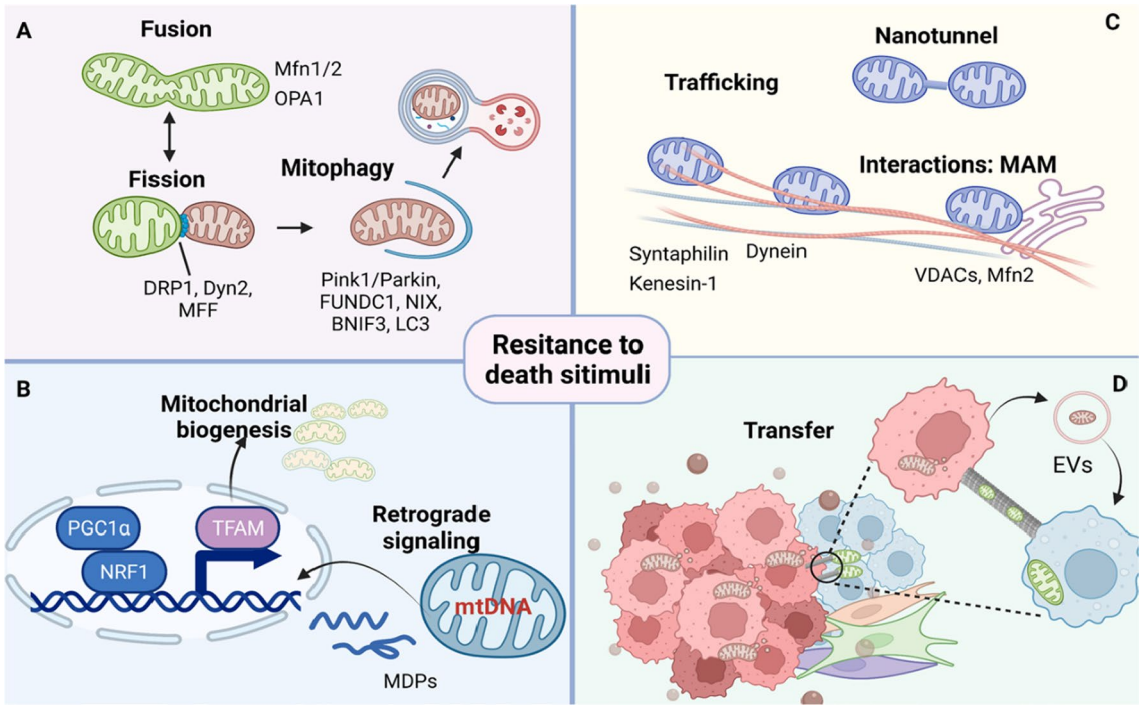

Fig. 2 Mitochondrial stress adaptation and drug resistance. Mitochondrial dynamics are processes related to mitochondrial stress adaptation. These processes maintain proper mitochondrial numbers, structure, and position to ensure their function and could foster cancer drug resistance. (**A**) Fusion and fission allow mitochondria to constantly form networks or fragments according to cellular metabolic requirements. Mitophagy has been shown to coordinate with fission, facilitating the elimination of excessive or defective mitochondria. (**B**) While mitochondrial biogenesis and functions are largely regulated by nuclear coding factors, recent advances have revealed that mitochondrial dysfunction activates retrograde (mitochondria-to-nucleus) signaling to modify nuclear gene expression and subsequent cell behavior. This mitochondrial retrograde signaling functions as an adaptive mechanism for tumor cells to sense and mitigate mitochondrial stress. (**C**) Reshaping, localization, and motility of mitochondria along the microtubules facilitate mitochondria tethering with the ER or other organelles. (**D**) Recently described nanotunnel formation promotes component exchange and transfer of intercellular mitochondria, which usually increase OXPHOS output and ATP production of recipient cells and confer them with a survival advantage

metastatic cancer cells with phenotypic and metabolic plasticity for survival in intravascular transit and distant sites [80]. Taken together, the complex structures confer the diverse functions of mitochondria, whose dysfunction may regulate several aspects of cancer onset and progression, indicating a promising therapeutic target.

Mitochondrial stress adaptation and drug resistance

Mitochondrial metabolic plasticity contributes to resistance in most types of anticancer therapy, as emphasized above [81, 82]. It is well orchestrated as a prerequisite of maintenance of OXPHOS, balance of ROS for signaling or defense, Ca^{2+} homeostasis, and proper induction of the apoptotic cascade. Mitochondrial dynamics modulate their shape, number, quality, and distribution in response to treatment and allow the maintenance of functional mitochondria (Fig. 2) [83]. Mitochondrial biogenesis and turnover, fusion and fission are universal mitochondrial stress-adaptive processes and have been well demonstrated to be involved in cancer drug resistance. Recent advances have expanded the paradigm of mitochondrial dynamics into mitochondrial trafficking and transfer, mitochondrial interplay with other organelles, and mitochondrial retrograde signaling [55, 84, 85]. These processes provide mitochondria plasticity for tumor cells, enabling tumor cells to survive under stress conditions, including radiotherapy and chemotherapy. In addition, the membrane system is essential for mitochondrial integrity to make the mitochondrial network more efficient in providing energy and required macromolecules. In this section, we systematically review the engagement of mitochondrial dynamics in cancer drug resistance.

Mitochondrial biogenesis and turnover in drug resistance

Mitochondrial biogenesis and turnover are two opposing processes that work in concert to regulate mitochondrial mass, function, and quality regulating the biogenesis of new mitochondria and the removal of

damaged mitochondria in a time-dependent manner. Mitochondrial biogenesis is regulated by the coordinated transcription of mitochondrial nuclear genes, in which PGC-1α plays a central regulatory role [86]. Reduced cellular bioenergetic output usually triggers mitochondrial biogenesis by activating AMPK to furnish OXPHOS and ATP production. In addition, oncogenes such as K-Ras and C-Myc are also involved in regulating mitochondrial biogenesis and increasing intracellular biosynthesis and respiration, thereby promoting tumorigenesis [87]. In particular, c-Myc controls the transcription of approximately 400 mitochondrial-related genes, thus regulating mitochondrial biogenesis [88]. These transcription networks provide metabolic flexibility for cancer cells to facilitate their adaptation to a hostile microenvironment and ultimately reduce the effectiveness of tumor treatment.

The most well-studied regulator involved in tumor drug resistance is PGC-1α, which facilitates tumor cell survival and metastasis under environmental stress by mediating mitochondrial biogenesis and OXPHOS [89, 90, 92]. Previous studies found that mutations in B-Raf or N-Ras in melanoma confer chemoresistance to MEK inhibitors by switching the metabolic mode to OXPHOS through upregulating PGC-1α or TFAM (transcription factor A, mitochondrial) to meet their bioenergy requirements [91, 93]. Similarly, upregulation of mitochondrial biogenesis and OXPHOS could augment tolerance to stimuli such as radiotherapy and ultraviolet radiation [94]. These studies demonstrate the critical role of adaptive mitochondrial biogenesis in drug-resistant capacity and highlight the potential of targeting mitochondrial OXPHOS for improving drug efficacy.

The maintenance of mitochondrial quality is also ensured by mitophagy, a programmed degradative process for eliminating excessive or defective mitochondria. Generally, the "eat me" signal on damaged mitochondria directly triggers mitophagy machinery by membrane depolarization and a cascade of phosphorylation and ubiquitination events to remove cytotoxic cellular components and maintain energy balance in the cell. It shares a common core mechanism with macro-autophagy but depends on specific mitophagy receptors, including the classical PTEN-induced putative kinase 1 (PINK1)-Parkin pathway [95, 96], and several other receptors, including Bcl-2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3/NIX), FUN14 domain-containing protein 1 (FUNDC1), and Bcl-2-like protein 13 (BCL2L13). While these receptors have been well demonstrated to elicit mitophagy and facilitate tumor progression [97–99], they were proven to confer resistance of cancer cells to a variety of commonly used chemotherapy drugs, such as 5-fluorouracil (5-fu), cisplatin, and doxorubicin (Dox), by triggering mitophagy [64, 100, 101]. For example, the highly activated ATAD3A-PINK1/Parkin signaling pathway under hypoxic conditions confers tolerance of liver cancer cells to sorafenib [102]. In esophageal squamous cell carcinoma (ESCC) patients, PINK1-mediated mitophagy promotes tumor cell survival under neoadjuvant therapy [103]. Interestingly, PINK1 could recruit ARIH1, rather than Parkin, to trigger mitophagy and ultimately lead to drug resistance in breast and lung cancer cells [104]. Several other emerging receptors, such as FUNDC1 and Galectin-1, have been reported to be upregulated to promote resistance to cisplatin and ionizing radiation by eliciting mitophagy [105]. In addition, the upregulation of these receptors relies on a series of stress-adaptive transcriptional programs mediated by p53, NF-κB, and STAT1/2 [106]. It would be of interest to further explore the regulatory role of these networks in regulating mitophagy and their potential role in drug resistance.

Mitochondrial fusion and fission in drug resistance

Mitochondrial fusion and fission allow mitochondria to constantly form networks or fragments according to cellular metabolic requirements. In general, fusion is commonly triggered by huge energy requirements, mediated by dynamin-related GTPases, optic atrophy 1 (OPA1) for IMM and mitofusin (MFN) 1 and 2 for OMM, resulting in a hyperfused mitochondrial network with increased mtDNA integrity, mitochondrial respiration, ATP production, and mitochondrial membrane potential (MMP) [107, 108]. Mitochondrial fission is mainly mediated by dynein-related protein 1 (DRP1) and fission protein homologous protein 1 (FIS1) and has been shown to coordinate with mitophagy or apoptosis, facilitating the elimination of damaged mitochondria, the redistribution of mtDNA, and the mobility of mitochondria [109–113]. These two opposing processes are tightly organized in response to stressors, thus engaging in tumor progression in a context-dependent manner [114–116]. For instance, the increase in mitochondrial fission caused by hypoxia has been shown to enhance the invasion of breast cancer [117].

Recent advances in mitochondrial medicine highlight the engagement of mitochondrial fusion and fission in mediating metabolic adaptation to chemotherapeutic agents in tumor cells. The relevance of mitochondrial fusion in chemoresistance is primarily evidenced by the upregulation of OPA1 and MFN1/2 expression, as well as interconnected mitochondrial networks in drug-resistant cancer cells. For instance, upregulated OPA1 confers resistance to cytochrome c release upon prolonged venetoclax treatment in acute myeloid leukemia (AML) cells [118]. Consistently, upregulated MFN2 and increased

OXPHOS have been found in cancer cells that survive chemotherapy [119, 120]. Several other factors have been reported to promote cancer drug resistance by triggering mitochondrial fusion. For example, circulating leptin protein activates induced myeloid leukemia cell differentiation protein (MCL1, a member of the anti-apoptotic protein BCL2 family) to induce mitochondrial fusion, thereby promoting tumor cells to survive during gemcitabine treatment [121].

Increasing evidence also shows the pivotal role of mitochondrial fission in chemoresistance [60, 122]. One of the best examples is that phosphorylation of DRP1 induces mitochondrial fragmentation to promote metabolic adaptation, thus protecting cancer cells from chemotherapy agents [123–125]. Phosphorylation or activation of several upstream kinases, such as AMPK, cyclin B1/Cdk1, ERK1, and DRP1, is involved in mitochondrial fission-mediated chemoresistance [61, 126]. Since mitochondrial fusion and fission represent two opposing systems, their balance and role in cellular fate are carefully orchestrated by specific cellular metabolic requirements. Therefore, more insights into the regulatory patterns of mitochondrial fusion and fission and their effect in chemotherapy are necessary to develop therapies offering improved clinical outcomes for cancer patients.

Inter-organelle contact sites, mitochondrial trafficking, and transfer in drug resistance

Mitochondria dynamically form contacts with various intracellular organelles to maintain cell homeostasis by fine-tuning Ca^{2+} transfer, phospholipid biosynthesis, ROS signaling, mitochondrial quality control, and mtDNA synthesis [127–133]. Such cellular membrane interactions are extensive and play the essential role in cell adaptation to metabolic stress [134].

The mitochondrial-associated endoplasmic reticulum (ER) membrane (MAM) is the most well-studied membranous system coordinating with a series of proteins and factors to maintain proper mitochondrial Ca^{2+} uptake which correlates with resistance to chemotherapy [135]. Mitochondrial Ca^{2+} uniporter complex (MCUC) subunits (MCU, MICU1, MICU2, EMRE, and MCUb) cooperate to maintain mitochondrial Ca^{2+} homeostasis, and their relevance to drug resistance is condition dependent [136–139]. For example, downregulation of MCU was demonstrated to confer resistance by restricting the transport of Ca^{2+} to the mitochondria in HeLa cells [140]. However, the interaction of MCU with receptor-interacting protein kinase 1 (RIPK1) can increase mitochondrial Ca^{2+} uptake, resulting in increased proliferation of colorectal cancer cells [141]. Additionally, MCUR1-mediated mitochondrial Ca^{2+} signaling was reported to facilitate cell survival of hepatocellular carcinoma (HCC) upon pro-apoptotic stimuli [137]. Several other recognized mitochondrial proteins, such as MFN2 and voltage-dependent anion-selective channel proteins (VDACs), were identified as important MAM proteins that might be involved in tethering MAMs and facilitating mitochondrial fission, mitophagy, and mitochondrial positioning [142, 143]. Moreover, there is mitochondrial contact with other organelles, such as peroxisomes, and lipid droplets, in response to metabolic stress. For example, "lipid droplet mitochondria" can help mitochondria provide energy by burning fatty acids (FAs) to support the TCA cycle [144]. Therefore, we conclude that exploring mitochondria-associated tethering systems could expand the understanding of mitochondrial dynamics and provide new targets for tumor intervention.

The proper localization of organelles is often crucial to their activity and function [145]. Numerous studies have shown that the movement and subcellular location of mitochondria can affect tumor cell polarity, morphology, and mobility capacity [146–150]. Mitochondrial stress responses drive strategic mitochondrial redistribution to fulfill bioenergetic needs, Ca^{2+} homeostasis, ROS buffering, and signal transduction, thus promoting the adaptation of tumor cells to the harsh tumor microenvironment [150–156]. A typical example is that of mitochondria migrating to the invasive front of metastatic tumor cells [157]. For example, the NF-κB-inducing kinase (NIK)-DRP1 axis could mediate the fission and subsequent directionally positioning of mitochondria to the cell periphery to promote the migration of a variety of tumors [151, 158]. In addition, the trafficking of mitochondria along the cytoskeleton could protect cells from detrimental ROS production [155, 159]. Notably, mitochondrial trafficking occurs to endow tumor cells for survival and metastasis upon drug abuse [160]. For instance, activated Akt promotes mitochondria positioning along the cytoskeleton to provide an effective "regional" energy source, thus fueling resistance and even adaptive cell invasion in response to PI3K inhibitors [148]. Intensive studies on this "spatiotemporal" model of mitochondria may deepen our understanding of the subcellular accumulation of mitochondria as an adaptative process and may provide a viable strategy to increase anticancer efficacy in the clinic.

Recent studies have shown that mitochondrial dynamics are accompanied by intercellular mitochondrial transfer [161–163]. This transfer process is achieved through several mechanisms, including gap junctions, extracellular vesicles (EVs), and tunneling nanotubes (TNTs) [164–169]. TNTs, the transient cytoplasmic extensions, are the major cellular structure that mediate intercellular mitochondrial transfer [170]. The mitochondrial transfer process usually increases the OXPHOS output and ATP

level of recipient cells. As a consequence, recipient cancer cells exhibit a survival advantage and resistance to stress [171–173]. Moschoi et al. observed that AML cells acquire intact mitochondria from marrow stromal cells (MSCs) to maintain their own mitochondrial function and survive during cytarabine treatment [174]. Several other tumors can also despoil mitochondria from MSCs and obtain resistance to chemotherapeutics [172]. In addition, it has been proposed that mitochondria transfer from bone marrow stromal cells (BMSCs) to multiple myeloma (MM) cells, which can also contribute to chemoresistance [175, 176]. Consistently, in breast cancer, mitochondrial transfer promotes resistance to doxorubicin [177], and mtDNA in exosomes derived from hormonal therapy-resistant breast cancer cells leads to endocrine therapy resistance. Intercellular transfer of mitochondria expands the influence of mitochondria on tumor metabolism, suggesting that targeting mitochondrial transfer could represent a more reasonable and effective antitumor strategy.

Mitochondrial retrograde signaling in drug resistance

Mitochondrial dynamic changes are positively regulated by nuclear coding factors, while recent advances underline that retrograde signaling activated by mitochondrial dysfunction can modify nuclear gene expression and subsequent cell behavior [59, 178]. In fact, it serves as an adaptive mechanism for tumor cells to sense and mitigate mitochondrial stress, thus participating in tumor survival, metastasis, and drug resistance.

Retrograde reactions

The signals from mitochondrial dysfunction, especially mutation/deletion in mtDNA, are usually relayed to the nucleus by TCA cycle intermediates, ATP, Ca^{2+} or ROS, which activate specific kinases to initiate transcriptional regulation of nuclear genes or posttranslational modification of key proteins (e.g., histone acetylation) [179–181]. The most well-studied example is the activation of AMPK triggered by a decrease in ATP levels, which elicits PGC-1α-mediated transcription of genes responsible for energy metabolism, mitochondrial synthesis, and the quality control system [182, 183].

As mentioned above, mitochondria are essential for maintaining intracellular Ca^{2+} levels. Disruption of MMP caused by deletion of the electron transport chain complex or drug insult led to leakage of Ca^{2+} into the cytoplasm. Intracellular free Ca^{2+}, on the one hand, activates multiple oncogenic signaling pathways, including RAC-alpha serine/threonine-protein kinase (AKT) and phosphatidylinositol 3-kinase (PI3K), to upregulate the expression of glucose transporters, such as GLUT1 and GLUT4, thereby promoting the metabolic switch to glycolysis and the survival of cancer cells [184–186]. On the other hand, Ca^{2+} signaling activates NF-κB and T cell nuclear factor (NFATC) signaling to facilitate the transcription of Ca^{2+} transport and storage-related proteins [187, 188].

ROS can directly manipulate cellular redox homeostasis and act as second messengers to regulate cellular physiological and pathological processes [189–191]. For example, ROS elicited by mtDNA depletion could activate the NRF2 signaling pathway and the multidrug resistance proteins MRP1 and MRP2 to help tumor cells fight against ROS and survive under cisplatin, doxorubicin, and SN-38 treatment [192]. In addition, ROS modulate the expression of PGC-1α to promote OXPHOS, thus conferring cisplatin resistance in ovarian cancer cells [193]. Together, these studies have linked mtDNA mutations/deletion with changes in sensitivity of cancer cells to chemotherapy, thus providing a new perspective on modulating drug resistance.

Mitochondrial nuclear feedback and mitochondrial stress-relieving response

Mitochondria have evolved protein quality control systems to maintain mitochondrial integrity by ensuring proper folding, assembly, and circulation of mitochondrial proteins in response to exogenous or endogenous stressors. This process tightly relies on feedback regulatory loops, including the mitochondrial unfolded protein stress response (UPR^{mt}) [194], proteolytic stress responses [195], and the heat shock response of mitochondrial chaperones [196]. These mechanisms are deregulated due to altered signaling to confer cancer cell survival, which ultimately contribute to tumor progression and drug resistance. This could be due to several proposed mechanisms, including continuous activation of NF-κB and molecular chaperone systems and mutations in the catalytic sites that contribute to resistance to proteasome inhibitors. For instance, a recent study has suggested that the mitochondrial oxidoreductase ferredoxin 1 (FDX1) maintains mitochondrial metabolism to promote the adaptation of tumor cells to the proteasome inhibitor elesclomol [197]. More investigations revealing the mechanisms employed in the quality control system of mitochondrial protein might offer unique strategies for improving therapeutic efficacy in cancer treatment.

Mitochondrial-derived peptides

Recently, mitochondria-derived peptides (MDPs, short open reading frames (sORFs) of mitochondrial genome) have been identified and implicated in stress response, metabolic regulation, and other biological processes. In response to cellular stress, these peptides can even directly manipulate nuclear gene expression [198], which

expands the paradigm of mitochondrial nuclear communication. Several MDPs have been identified, including Humanin [199], humanin-like peptides (SHLP) 1–6 [200], and MOTS-c [201–203]. Among them, humanin was reported to protect cells from oxidative stress and mitochondrial dysfunction [204]. SHLP2 and SHLP3 exert similar cytoprotective effects by maintaining mitochondrial function and combating excessive ROS levels [202, 205]. In particular, MOTS-c was reported to translocate to the nucleus under metabolic stress such as glucose deprivation and oxidative stress [206]. In the nucleus, MOTS-c regulates the transcription of a broad range of genes, including those with antioxidant response elements (AREs) and other anti-inflammatory-associated genes, to initiate the stress adaptation program. A considerable number of studies have now proven that MDPs are intrinsically linked to tumor progression, and targeting MDPs holds potential to improve the efficacy of chemotherapeutics [207, 208].

Mitochondria-mediated CSC properties in drug resistance

It is well established that CSCs contribute substantially to the refractory features of cancer. Under pharmacological treatment, mitochondria function as a central hub to maintain the survival and self-renewal capacity of CSCs, resulting in drug resistance and tumor recurrence [209]. For example, it has been reported that oncogenic Myc cooperated with MCL1 to maintain chemoresistance of CSCs in triple-negative breast cancer (TNBC). Further studies found that Myc and MCL1 upregulated the levels of mitochondrial OXPHOS and promoted ROS generation, which contributed to the accumulation of HIF-1α and the subsequent maintenance of CSC properties [210]. Moreover, PGC-1α, a critical regulator of mitochondrial biogenesis, has been demonstrated to enhance stem cell-like characteristics and chemoresistance to cisplatin in ovarian cancer [211]. In addition, increased levels of mitochondrial mass were found in a subtype of chemo-resistant breast cancer cells enriching in several known CSC markers, implying the potential of targeting mito-high CSC population for cancer therapy [212]. Therefore, investigation of mitochondrial function in regulating CSCs holds the promise to benefit the development of novel CSC-targeted strategies for reversing cancer drug resistance.

In summary, a large body of evidence has indicated the important role of mitochondrial dynamics in the adaptative mechanism of cancer cells in response to a challenging environment, which is expected to expand the understanding of cancer drug resistance phenomena [91, 213–216]. Further investigations deciphering specific mitochondrial-related mechanisms implicated in the resistance could hopefully benefit the identification of possible biomarkers for the early prediction of cancer drug resistance and hold promise to target mitochondria for overcoming cancer drug resistance.

Targeting mitochondria to overcome cancer drug resistance: the current status and challenges

The mitochondrial ETC fuels cellular energy demands by utilizing intermediates from various metabolic pathways, including the TCA cycle and FAO, and couples the generation of macromolecules such as amino acids and nucleotides [217–219]. Thus, dynamic regulation of mitochondria involves robust metabolic and redox alterations, as well as changes in ion (e.g., Fe^{2+}, Ca^{2+}) homeostasis. Increasing knowledge that these critical processes are linked to tumor transformation makes mitochondria an attractive therapeutic target. In this section, we will summarize current mitochondrial therapeutic targets and their proposed inhibitors (Fig. 3, Table 1), with a particular emphasis on the role of small-molecule inhibitors in targeting mitochondria to overcome cancer chemoresistance.

Targeting mitochondrial ETC

The mitochondrial ETC complexes I–V (hereafter CI-V) bypass electrons to generate energy and are the major source of mitochondrial ROS [250, 251]. Disruption of the ETC inevitably triggers apoptosis and perturbs the cellular redox balance and therefore provides a possible strategy for eliminating cancer cells [252].

Complex I

Mitochondrial complex I (CI), the largest complex of the ETC, transfers TCA cycle-derived electrons from NADH from the UbQ and maintains the proton gradient on the MIM. Several inhibitors including piericidin, tamoxifen, metformin, and ME-344 that directly target the respiratory complex I have gained momentum as potential antitumor therapeutics. Metformin, an antidiabetic drug has now been repurposed as an anticancer drug and was observed to inhibit CI. Many preclinical and clinical studies have demonstrated its excellent antitumor efficacy in managing resistance caused by chemotherapeutics, including cisplatin, Dox, and 5-FU (NCT00897884, NCT02437656; Table 2) [253–256]. In addition, a recent phase II clinical trial observed that combinational use of metformin with standard epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy significantly improved both progression-free survival and overall survival in patients with advanced lung adenocarcinoma (NCT03071705; Table 2) [257]. Consistently, metformin-sensitized lymphoma to isocitrate dehydrogenase (IDH) mutant inhibitors and increased the sensitivity of lymphoma to AZD3965, a monocarboxylate

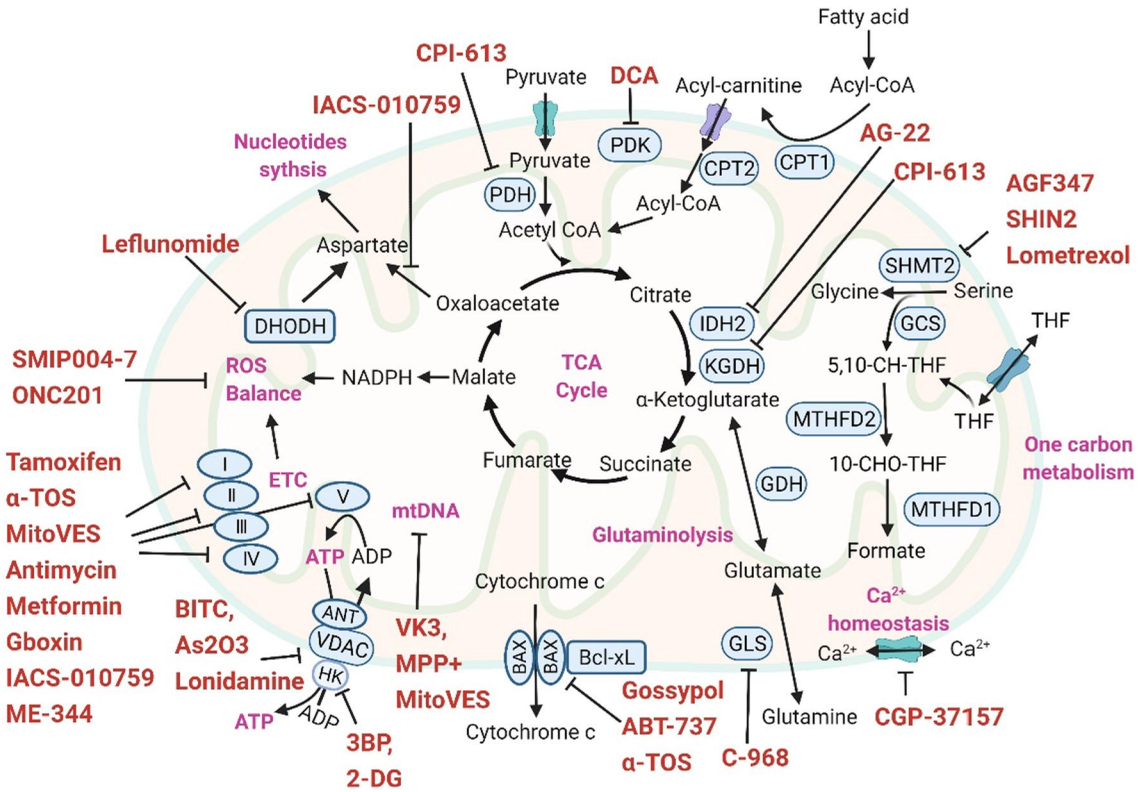

Fig. 3 Schematic showing representative mitochondrial therapeutic targets and their proposed inhibitors. The mitochondrial ETC, as the central system of mitochondrial energy production and OXPHOS, has been the most frequently used mitochondrial target. Multiple mitochondrial ETC inhibitors, including metformin and IACS-010759, are being investigated for cancer treatment. In addition, inhibitors targeting different steps of the mitochondrial TCA cycle have shown promise in phase I and II clinical trials. Several other TCA cycle-coupled biomacromolecule synthesis pathways, such as the nucleotide synthesis pathway and the one-carbon (1C) metabolic pathway, are also potential therapeutic targets for reversing drug resistance

transporter (MCT1) inhibitor, by disturbing mitochondrial complex I and bioenergetics, thus providing a scientific rationale for combinatory mitochondrial-targeted therapies to overcome drug resistance in human lymphoma [53, 258].

Complex II

Complex II (CII, succinate dehydrogenase), the smallest respiratory complexes, is a membrane-bound component of the TCA cycle that permits the oxidation of succinate to fumarate. Compounds that induce substantial ROS generation from CII are the emerging anticancer drugs. For example, alpha-tocopheryl succinate (α-TOS), a compound targeting UbQ-binding sites in CII, has been demonstrated to disturb CII for eliciting mitochondrial permeabilization and apoptosis, thus showing significant potential in overcoming drug resistance in various tumors [226, 259, 260]. In particular, based on the knowledge that α-TOS targets UbQ-binding sites, a more specific mitochondrial-targeted analogue, MitoVES, was designed for efficiently suppressing tumors by disturbing mitochondria [261, 262].

Complex III

CIII, similar to CI, functions by pumping protons across the MIM and contributing to the proton gradient. It has been also identified as target for anticancer drugs. Antimycin A is the most classic CIII inhibitor to trigger apoptosis for effectively eliminating cancer cells [263, 264]. Resveratrol, a plant-derived polyphenol, exhibited considerable antitumor efficacy by efficiently inhibiting ETC complexes, especially CIII to induce apoptosis and disturb multiple cellular processes in primary and resistant cancer cells [265–267]. Importantly, the anticancer potential of resveratrol is being investigated in clinical trials for the treatment of colorectal, liver, and breast cancer (NCT0025633, NCT00433576, and NCT03482401; Table 2).

Table 1 Summary of mitochondrial targets for cancer therapy

Category (Mitochondria signaling pathway)	Targets	Inhibitors and Refs
Mitochondrial ETC and OXPHOS	Complex I	Piericidin [220]; rotenone [221]; deguelin [222]; tamoxifen [123, 223]; metformin [224]; ME-344 [225]
	Complex II	α-TOS [226]; MitoVES [227]
	Complex III	Resveratrol [228];
	Complex IV	Fenretinide [229];
	Complex V	BZ-423 [230]
Targeting the mitochondrial metabolic pathway	Heme synthesis	Cyclopamine tartrate (CycT) [231]; HasA [232]
	1C metabolism (SHMT1 and SHMT2)	AGF291, AGF320, and AGF347 [233, 234]; lometrexol [235]
	DHODH	leflunomide [236, 237]
	Nucleotide biosynthesis	IACS-010759 [238]
	TCA cycle (α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (PDH)	CPI-613 [239]
	Glutaminase (GLS)	CB-839 [240], bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide (BPTES) [241]
	Glutamate-pyruvate transaminase 2 (GPT2)	Aminooxyacetate (AOA) [54]
Redox balance	NADH:ubiquinone oxidoreductase	SMIP004-7 [242];
Ca^{2+} homeostasis	VDACs and ANT	lonidamine[243], steroid analogs [244]
	Na^{+}/Ca^{2+} exchanger	CGP-37157 [245]
	Bcl-2	Gossypol [246]
	S100A4	Niclosamide [247]
Mitochondrial membrane proteins	Hexokinase II	3-bromopyruvate [248]; 2-Deoxyglucose (2-DG) [249]

Complex IV

CIV ensures the final step of electron transport in ETC to maintain the proton gradient and mitochondrial membrane potential. Several compounds have been observed to modulate the mRNA or protein expression of CIV subunits and thereby induce apoptosis in tumor cells. Fenretinide (also named as N-(4-hydroxyphenyl) retinamide, 4-HPR) and its analogue are perhaps the most well-documented category to downregulate CIV by destabilizing the mRNA transcript [268], thereby inducing ROS-mediated apoptosis to combat tumors in both preclinical and clinical studies (NCT00004154, NCT00009971, and NCT00077402; Table 2) [269, 270]. In particular, Fenretinide has been reported to eliminate ABT-737-resistant cell lines via ROS generation and MCL1 reduction and thus has synergetic effect with ABT-737 to enhance mitochondrial apoptotic cascade in acute lymphoblastic leukemia (ALL) [271].

Complex V

CV, the ATP synthase, directly catalyzes ATP production using the proton gradient maintained by complexes I–IV, thus supplying the cell with essential energy. Besides oligomycin and its derivatives, several newly identified CV inhibitors, including 3,30-diindolylmethane (DIM), Bz-423, were proposed to fight tumors and even those with drug resistance [230, 272]. Notably, there are compounds that could inhibit different complexes of ECT. For example, resveratrol is also reported to bind to CV and induce Bcl-2-mediated apoptosis [273]. In addition, Gboxin, an OXPHOS inhibitor, is observed to interact with several respiratory chain proteins spanning CI, CII, CIV, and CV, thereby suppressing tumor growth [274]. Although it remains to be known whether these ETC inhibitors will be effective in humans, emerging studies provide excellent prospects for their application in cancer therapy and drug resistance eradication.

Mitochondrial redox balance

ROS are intrinsically involved in tumor progression by modulating cell survival, secondary signaling networks, and genetic instability/mutations [275]. Mitochondria function as a major contributor to endogenous ROS due to the large electron flow in the ETC and constant metabolism alterations involved in numerous enzyme-catalyzed reactions. Mitochondrial redox balance is typically mediated by cellular antioxidants, such as glutathione (GSH), glutathione peroxidases (GPx1 and GPx4), and glutathione reductase [276–282]. Emerging observations suggest that heightened levels of ROS contribute to drug resistance. For instance, gefitinib resistance was demonstrated to be associated with mitochondrial dysfunction

Table 2 Clinical trials of identified mitochondrial inhibitors

Inhibitor	Target	Cancer type	ClinicalTrials.gov Identifier	Status
Metformin	CI	Breast cancer	NCT04559308	Recruiting
		Breast cancer	NCT00897884	Completed
		Rectal cancer	NCT02437656	Completed
		etc.		
VLX600	ETC	Refractory cancer	NCT02222363	Terminated
Fenretinide	CIV	Advanced or metastatic hormone refractory prostate cancer	NCT00077402	Completed
		Lung cancer	NCT00009971	Completed
		Bladder cancer	NCT00004154	Completed
		etc.		
Resveratrol	CIII	Colon cancer	NCT00256334	Completed
		Liver cancer	NCT00433576	Completed
		Breast cancer	NCT03482401	Completed
		etc.		
Tigecycline	Mitochondrial ribosomal machinery	Acute myeloid leukemia	NCT01332786	Completed
Gamitrinib	Mitochondrial chaperone proteins, such as TRAP-1 and HSP-90	Lymphoma, advanced solid tumor	NCT04827810	Recruiting
CPI-613	TCA cycle, PDH	Biliary tract cancer	NCT04203160	Recruiting
		Advanced hematologic malignancies	NCT01034475	Completed
		Recurrent small cell lung cancer	NCT01931787	Completed
		etc.		
Dichloroacetate	PDK	Head and neck cancer	NCT01163487	Completed
		Squamous cell carcinoma of the head and neck	NCT01386632	Completed
		etc.		
IACS-010759	CI, TCA cycle	Advanced malignant solid neoplasm; Anatomic stage IIIA breast cancer	NCT03291938	Completed
		Recurrent acute myeloid leukemia	NCT02882321	Active, not recruiting
		etc.		
Leflunomide	DHODH	Breast neoplasms	NCT03709446	Recruiting
		Prostate cancer	NCT00004071	Completed
		Brain and central nervous system tumors	NCT00003775	Completed
		etc.		
ONC201	OXPHOS	Endometrial cancer recurrent	NCT03485729	Recruiting
		Triple-negative breast cancer; endometrial cancer; hormone receptor positive, HER2 negative breast cancer	NCT03394027	Completed
		Recurrent neuroendocrine tumor; metastatic neuroendocrine tumor	NCT03034200	Active, not recruiting
		etc.		
Tamoxifen	ETC	Breast cancer	NCT00286117	Completed
		Estrogen receptor positive breast cancer	NCT02988986	Completed
		Bladder cancer	NCT02197897	Completed
ME-344	ETC	Breast cancer; human epidermal growth factor 2 negative carcinoma of breast; early-stage breast carcinoma	NCT02806817	Completed
		etc.		
Gossypol	Bcl-2 family proteins	Extensive stage small cell lung cancer; Recurrent small cell lung cancer	NC T00666666	Completed
		etc.		
Lometrexol	SHMT2	Lung cancer;	NCT00033722	Unknown
		Unspecified adult solid tumor, protocol specific	NCT00024310	Unknown

in lung cancer cells [283]. Conventional chemotherapies, such as 5-FU and cisplatin, are designed to kill cancer cells via ROS-dependent mechanisms. In that context, enhanced ROS levels could maximize antitumor efficacy. For example, SMIP004-7 targets NADH:ubiquinone oxidoreductase to improve the immunotherapeutic effect of PD-1 in triple-negative breast cancer [242]. Destroying the redox balance is perhaps the essence for modulating mitochondrial ROS to benefit cancer therapy. In view of this, redox status during treatment and the basal mitochondrial ROS range may provide important clues for guiding rational intervention strategies. Selective targeting of ROS-specific organelles, as well as dynamic ROS delivery, might be beneficial for preventing drug resistance and effectively eliminating cancer cells.

Targeting the mitochondrial metabolic pathway

Nucleotide biosynthesis

Targeting mitochondrial ETC-linked metabolic pathways, such as nucleotide metabolism, also contributes to improved antitumor efficacy. One-carbon (1C) metabolism coordinates with serine synthesis to provide glycine and tetrahydrofolate methyl donors, namely methylene-THF (5,10-CH-THF) and formyl-THF (10-CHO-THF), for nucleotide synthesis. As essential enzymes in 1C metabolism, cytosolic SHMT1 and mitochondrial SHMT2 have attracted much attention. Several inhibitors, including AGF291, AGF320, and AGF347, have been developed to target these enzymes, and their antitumor efficacy has been established for lung, colon, and pancreatic cancer cells [233, 234, 284]. Intriguingly, folate inhibitors such as lometrexol have also been found to reduce SHMT1 and SHMT2 activity [235]. Several clinical trials are undergoing to investigate the use of lometrexol in advanced solid tumor (NCT00033722 and NCT00024310; Table 2).

In addition, efforts have been made to inhibit nucleotide metabolic enzymes, such as the intramitochondrial key pyrimidine synthesis-related enzyme, dihydroorotate dehydrogenase (DHODH). Leflunomide exhibited antitumor activity in prostate cancer mouse model by inhibiting DHODH [236]. Additionally, a phase I clinical study showed leflunomide had considerable activity toward myeloma with manageable side effects (NCT02509052; Table 2). Furthermore, IACS-010759, a mitochondrial CI inhibitor, was developed to induce apoptosis in brain cancer and AML, likely caused by energy depletion and reduced aspartate production that led to impaired nucleotide biosynthesis [238]. Combinational use of IACS-010759 with lactate dehydrogenase (LDH) inhibitor could overcome oxidative rewiring and show a synergistic therapeutic effect [49]. Key enzymes involving in nucleotide metabolism could also play a "part-time role" in other mitochondrial processes (e.g., SHMT2 participating in mitochondrial translation) [285–287]. The antitumor effects of nucleotide metabolism inhibitors could be manifold. As such, further efforts are urgently needed to screen for candidates targeting nucleotide metabolism for cancer management.

TCA cycle

The mitochondrial TCA cycle integrates multiple fuel sources to synthesize nucleotide, amino acid, lipid, and heme. Several TCA cycle inhibitors have been under investigation and predicted to be efficacious. Among them, CPI-613, a lipoate analog that targets two enzyme complexes of the TCA cycle (α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (PDH)) [288], exerts anticancer activity in pancreatic cancer and AML [289]. Notably, CPI-613 could sensitize AML cells to cytarabine and mitoxantrone, representing a promising approach for relapsed or refractory AML [239]. To date, clinical trials of CPI-613 for the treatment of advanced or recurrent tumor are ongoing, or have already been completed with satisfactory results (NCT04203160, NCT01034475, and NCT01931787; Table 2). Interestingly, a recent study reported that vitamin C modulates the activity of PDH and regulates the TCA cycle via interfering with PDK1-mediated phosphorylation of PDH in KRAS mutant colon cancer, suggesting a potential application for clinical management of chemoresistance to anti-EGFR therapy [290].

Glutaminolysis

Glutamine (Gln) can be converted to glutamate by glutaminase (GLS) and further metabolized to α-KG via glutamate dehydrogenase 1 (GLUD1), glutamate oxaloacetate transaminase 2 (GOT2) or glutamate-pyruvate transaminase 2 (GPT2), thus providing a major carbon source to replenish the TCA cycle [291–295]. Many classes of compounds that target mitochondrial Gln metabolism are being investigated for cancer treatment. GLS inhibitors have shown promising anticancer effect in preclinical models of cancer. For example, bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide (BPTES), a GLS inhibitor, has been demonstrated to slow the growth of various types of tumors [296, 297].

Importantly, BPTES was observed to efficiently sensitize pancreatic cancer to 5-(tetradecyloxy)-2-furoic acid (TOFA, an acetyl-CoA carboxylase inhibitor) and ß-Lap (an NADPH:quinone oxidoreductase (NQO1) inhibitor) via enhancing cancer cell apoptosis [241, 298, 299]. In particular, CB-839 (telaglenastat), another GLS inhibitor, has moved on to clinical trials and exhibits promise as potential drug for renal cell carcinoma (NCT03428217; Table 2), hematological malignancies (NCT03428217

and NCT02071888; Table 2), non-small cell lung cancer (NSCLC) (NCT02071862; Table 2), and even those drug-resistant tumors (NCT03944902 and NCT03798678; Table 2). Recently, GPT2 has been demonstrated to promote cell survival by supporting the TCA cycle after GLS inhibition [54]. In that context, inhibition of GPT2 using aminooxyacetate (AOA), a transaminase inhibitor, could thus sensitize cancer cells to BPTES.

Targeting Ca^{2+} homeostasis

Mitochondria have evolved Ca^{2+} influx and efflux systems to maintain cellular Ca^{2+} homeostasis. Proper mitochondrial Ca^{2+} ensures respiration efficacy and ATP production, while Ca^{2+} overload can induce mitochondria-mediated apoptosis [300–303]. Therefore, mitochondrial Ca^{2+} signaling pathways engage multifaceted roles in regulating cell fate and are beneficial for tumorigenesis. Studies are under way to identify the proteins involved in mitochondrial Ca^{2+} signaling pathways as alternative targets for cancer therapy, and to evaluate the potential for increasing the sensitivity toward chemotherapeutic treatment. Compounds that modulate mitochondrial porins such as VDACs and ANT, including lonidamine, arsenites, and steroid analogs, have been documented to disturb the mitochondrial Ca^{2+} balance and elicit mitochondrial apoptosis, thus showing potent antitumor efficacy as well as drug resistance overcoming activity [243, 244, 304]. In addition, a mitochondrial Na^{+}/Ca^{2+} exchanger inhibitor, CGP-37157, resulted in a persistent mitochondrial Ca^{2+} rise and may serve as a promising agent to overcome TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) resistance [245, 303]. In ovarian cancer cells, the overexpression of Bcl-2 attenuated cisplatin cytotoxicity by downregulating ER-mitochondrial Ca^{2+} signal transduction. Thus, targeting Bcl-2-mediated Ca^{2+} signal might be a potential approach to overcome drug resistance in ovarian cancer [305].

Current challenges in targeting mitochondria

The mitochondrion is perhaps the most challenging target for cancer therapy [306, 307]. The constant alterations in mitochondrial structure and position contribute greatly to the failure of targeted agents, the bias in drug toxicity, and drug dosage prediction [308]. For example, the doses of metformin that could reduce the proliferation of cancer cells in laboratory models (in vitro cell lines and in vivo mouse models) were 10- to 1,000-fold higher than those that are deemed safe clinically [309]. This makes it urgent to assess the efficacy and safety of higher doses of metformin to determine its clinical potential. Second, many mitochondrial inhibitors are delivered into the mitochondria depending on the MMP. As such, imported drugs could inhibit ETC complexes and diminish the MMP, leading to decreased total agent importation [310, 311]. In addition, targeting the ETC is likely to be fraught with severe side effects. Some ETC inhibitors are considered neurotoxic, such as rotenone [312, 313], and some, such as cyanide, are even lethally toxic [314, 315]. In particular, IACS-010759, a CI inhibitor being advanced to clinical trials (NCT03291938 and NCT02882321; Table 2) [238, 316], has been associated with neuropathy and visual changes [49]. Moreover, metabolic plasticity promotes cancer cells to shift their metabolic features upon targeting specific metabolic vulnerabilities [317]. Furthermore, the selection of metabolic targets for therapeutic intervention has often been done in cell culture systems, where the metabolism of initial tumor-derived cells may be significantly affected by culture conditions [318]. These systems also do not recapitulate tumor heterogeneity and complex intertumor and tumor–host interactions [47].

Strategies for overcoming mitochondria-targeting bottlenecks to combat drug resistance

As mentioned above, limitations in drug sources and drug targeting challenge the application of targeting mitochondria for improving therapeutic efficiency in cancer treatment. Therefore, researchers are seeking new strategies to achieve a competitive advantage in targeting mitochondria for cancer therapy. Redevelopment and reuse of old drugs (repurposing/repositioning) represent such an opportunity to replenish the inventory of mitochondrial-targeted antitumor drugs [224]. Besides, the use of targeted nanomedicines offers innovative therapeutic strategies to overcome multiple barriers and selectively transport drug molecules to the mitochondria [319, 320]. Additionally, mitochondrial transplantation is an emerging approach that exerts antitumor potential by restoring mitochondrial function [321].

Drug repurposing for overcoming mitochondria-targeting bottlenecks

Drug repositioning is a strategy to identify medications that were initially used for the treatment of other noncancer illnesses for tumor therapy, based on an accumulated understanding of their mechanisms of action [322–324]. The advantages of this approach include, but are not limited to, the already established pharmacokinetic, pharmacodynamic, and toxicity profiles, their rapid progress into clinical trials, the significantly lower associated development cost as well as a relatively less risky business plan [325–327]. In recent years, technological innovation combined with the development of big data repositories and the analytical methods, as well as the emergence of a variety of innovative computational methods and in

silico approaches, have greatly promoted the process of drug repurposing [328–331]. In this section, we present various promising repurposed non-oncology drugs that disrupt specific mitochondrial components and their functions for preclinical or clinical management of cancer drug resistance (Table 3).

Repositioning antidiabetic drugs

Metformin, an approved antidiabetic drug which has been used in cancer therapy, is one of the most successful repurposed drugs [332–335]. Several signaling pathways, including insulin/IGF1, NF-κB, AMPK/mTOR/PI3K, Ras/Raf/Erk, Wnt, Notch, and TGF-β signaling, have been identified to be involved in its antitumor effect [336–344]. Besides, metformin has been well demonstrated to target mitochondria and induce cytotoxic effects [345–348]. Numerous preclinical studies and clinical trials are investigating the therapeutic potential of metformin in many types of tumors [349–351]. Consistent with this, metformin was proven to enhance the anticancer effect of radio- or chemotherapies. For instance, Lee et al. observed that metformin could overcome resistance to cisplatin by downregulating RAD51 expression, representing a novel strategy in TNBC management [255]. In addition, in NSCLC, metformin acts synergistically with sorafenib to inhibit cell proliferation by activating AMPK, which holds significant potential to be tested in prospective clinical trials [352].

Other biguanides also exhibit enhanced antiproliferative or radio-sensitizing effects in cancer cells. For instance, HL156A, a metformin analog, markedly decreased MMP and induced ROS levels to activate caspase-3- and caspase-9-mediated apoptosis, thus suppressing tumor growth [353]. This study suggests the potential value of HL156A as a candidate for the treatment of oral cancer. Phenformin, a potent mitochondrial ETC inhibitor, also displayed remarkable anticancer activity against several tumors [354]. In colorectal cancer, phenformin could overcome hypoxic radio resistance through inhibition of mitochondrial respiration [355]. In breast cancer, phenformin synergistically decreased respiration and ATP production with oxamate, an inhibitor of lactate dehydrogenase, to inhibit tumor growth [356]. Furthermore, phenformin and oxamate displayed synergistic anticancer effects through simultaneously inhibiting mitochondrial complex I and cytosol LDH in this study.

Moreover, several other antidiabetic drugs have also been successively repurposed for cancer therapy and drug resistance management. Exendin-4 (Exe-4), a GLP-1 receptor agonist, was reported to elevate mitochondrial ROS and trigger subsequent apoptosis, which attenuated hyperglycemia-induced chemoresistance and sensitized human endometrial cancer cells to cisplatin treatment [357]. Canagliflozin, another antidiabetic drug, was identified to inhibit the proliferation of lung and prostate cancer cells, alone or in combination with ionizing radiation or chemotherapy using docetaxel by inhibiting mitochondrial CI supported respiration [358]. In addition, piperazine also targeted mitochondria to inhibit oxygen consumption, thus exhibiting an additive effect on inhibiting cell proliferation in combination with the glycolysis inhibitor 2-deoxyglucose (2-DG) [359].

Overall, repurposing antidiabetic drugs provides a plethora of candidates to suppress the growth of many types of tumors by targeting mitochondria. These drugs could not only increase the efficacy of standard therapies, but also reduce their side effects by potentially modulating metabolic plasticity.

Repositioning antimicrobial agents

Antimicrobial therapeutics, including antibiotics, anthelminthic and antifungal drugs, have been repurposed against tumors (e.g., breast, liver, colorectal and lung cancers, glioblastoma, multiple myeloma, and leukemia). A particularly important mechanism underlying their anticancer effects is interfering with mitochondrial function [360]. Examples of antibiotics that suppress cancer by altering mitochondria include the chloramphenicol family and tetracycline [361]. For instance, tigecycline preferentially inhibits the translation of mtDNA-encoded proteins to restrain the mitochondrial respiratory chain, causing mitochondrial dysfunction and increased oxidative stress, thus providing a therapeutic strategy for overcoming chemoresistance in human renal cell carcinoma and ovarian cancer [362, 363]. The antibiotic drug levofloxacin has also been repurposed to inhibit proliferation and trigger apoptosis of lung cancer cells by inducing mitochondrial dysfunction and oxidative damage [364].

In addition, several anthelminthic compounds were observed to interfere with mitochondria and combat with tumors. For instance, niclosamide could induce mitochondrial dysfunction and activate Bax and caspase-3, which attenuates migratory and invasive behaviors and promote apoptosis in thyroid cancer and chondrosarcoma tumors [365, 366]. Another anthelmintic drug, ivermectin, was suggested to inhibit angiogenesis, growth, and survival by decreasing mitochondrial respiration, membrane potential, and ATP levels [367]. The well-documented antimalarial agent artemisinin and its derivatives also possess potent anticancer activity through mitochondria-related pathways, manifesting as significantly reduced MMP, increased intracellular ROS and Ca^{2+} levels, and upregulated apoptosis-associated proteins [368, 369]. In particular, artesunate was reported to induce PINK1-dependent mitophagy to alter

Table 3 List of repurposed mitochondria-targeted drugs

Original application	Repurposed drug	Effects on mitochondria	Effects on cancer	Cancer type
Antidiabetes	Metformin	↓Complex I activity, ↓Respiration, ↓ATP production	↓Cell growth, ↑cell death, overcome chemoresistance	Breast cancer, colorectal cancer, lung cancer, ovarian cancer, etc.
	HL156A	↓MMP, ↑ROS, ↑caspase-3 and caspase-9	↑Apoptosis, antiproliferative, Radio sensitizing	Oral cancer
	Phenformin	↓Complex I, ↓respiration, ↓ATP production	Antiproliferative, radio sensitizing, overcome chemoresistance	Colorectal cancer, breast cancer
	Exendin-4 (Exe-4)	Mitochondrial dysfunction, ↑ROS,	Overcome chemoresistance	Endometrial cancer
	Canagliflozin	↓Complex I, ↓respiration	Antiproliferative, Radio sensitizing, overcome chemoresistance	Prostate cancer, lung cancer, etc.
	Pioglitazione	↓Oxygen consumption	Antiproliferative, overcome chemoresistance	Prostate cancer
Antibiotics	Tigecycline	↓mtDNA-encoded proteins, ↓Respiration	Overcome chemoresistance	Renal carcinoma, ovarian cancer
	Levofloxacin	Mitochondrial dysfunction, oxidative damage	Inhibit proliferation, induce apoptosis	Lung cancer
Anthelminthic	Niclosamide	Mitochondrial dysfunction, activated Bax and caspases-3	↑Apoptosis, ↓Migration, ↓Invasion	Thyroid cancer, chondrosarcoma tumor
	Ivermectin	↓Mitochondrial respiration, ↓Membrane potential, ↓ATP levels	Inhibit angiogenesis, ↓growth and survival	Glioblastoma
Antimalarial agents	Artemisinin	↓MMP, ↑ROS, ↑Ca^{2+}	Cell cycle arrest, ↑Apoptosis, Anti-angiogenesis	Colorectal cancer, breast cancer
	Artesunate	Mitophagy, ↓GSH, ↑ROS	↑Cell death	Cervical cancer
Antifungal agents	Itraconazole	VDAC1 inhibition, mitochondrial metabolism disruption	Inhibit angiogenesis, ↓Growth and survival	Breast cancer, liver cancer
	Ketoconazole	Mitophagy	Antiproliferative, overcome chemoresistance	HCC
	Econazole	Ca^{2+} channel inhibition, cytochrome c leakage	↑Cell death, Anti-tumorigenesis	Leukemia, colorectal cancer
Antihypertension	Prazosin	↓MMP,	Reduced tumor mass	Prostate
	Quercetin	↓MMP,	Antitumor, Radio sensitizing	Lung cancer, gastric cancer
	Lercanidipine	Mitochondrial Ca^{2+} overload, mitochondrial vacuolation	↑Apoptosis, chemosensitization	Breast cancer
	Telmisartan	Mitochondrial fission, ROS accumulation	↑Apoptosis, chemosensitization	Melanoma
Antidepressants	Imipramine	Stressed mitochondria restoration	Hijack aggressive character of cancer	Glioblastoma
	Amitriptyline	Stressed mitochondria restoration	Hijack aggressive character of cancer	Glioma
	Chlorimipramine	↓Complex III activity, ↓MMP, mitochondrial swelling and vacuolation	Antitumor	Glioma
	Fluoxetine	Mitochondrial dysfunction	Antiproliferative, overcome chemoresistance	Colorectal cancer, breast, Ovarian cancer
	Depression	Mitochondrial dysfunction	↑Apoptosis,	Bladder cancer
Antiepileptic drug	Valproic acid	↓Respiration, ↓ATP production, ↑ROS	Antiproliferative, Pro-apoptotic, chemosensitization	Thoracic cancer, lung cancer, colorectal cancer

Table 3 (continued)

Original application	Repurposed drug	Effects on mitochondria	Effects on cancer	Cancer type
Treatment for pain	Aspirin	Activated Bax and caspases-3, cytochrome c leakage	↑Apoptosis	Cervical cancer
Treatment for rheumatism	Indomethacin	Impairs mitochondrial dynamics	↑Apoptosis, chemosensitization	Lung cancer, gastric cancer, etc.
	Auranofin	Inhibits mitochondrial TrxR	Antiproliferative	Lung cancer, ovarian carcinomas
Treatment for stomachache, abdominal pain, rheumatism	Angelica polymorpha maxim root extract	↓MMP, activated Bax and caspases-3	↑Apoptosis	Neuroblastoma
Treatment for rheumatism, Liver cirrhosis	Euphorbia formosana Hayata (EF)	Mitochondria dysfunction	Tumor suppression	Leukemic cells
Treatment for thalassemia, Friedreich's ataxia kidney disease	Deferiprone	Suppress mitochondrial metabolism, ↓Respiration, ↑ROS	Antiproliferative, Reduce migration	Prostate, Breast cancer, etc.
Iron chelator	VLX600	↓Respiration, ↓ATP production	Antitumor, chemosensitization	Ovarian cancer, colorectal cancer, etc.
Copper overload disorder	Tetrathiomolybdate	↓Respiration, ↓ATP production	Inhibit angiogenesis, antitumor	Papillary thyroid cancer
Alcohol-aversion drug	Disulfiram	Mitochondrial fission, ↓MMP	Antitumor, chemosensitization	Melanoma, colorectal cancer
Copper-chelating agent	Elesclomol	Interacts with ETC, ↑ROS	↑Apoptosis	Colorectal cancer, leukemia, etc.
Palliative effects	Cannabinoids	Mitochondrial damage, ↑ROS	Reduce proliferation, induce apoptosis and autophagy, Inhibit invasion and angiogenesis, Improve chemosensitivity	Oral cancer, Lung cancer, etc.

the cellular redox status in HeLa cells [370]. In addition, atovaquone, another antimalarial agent, can inhibit mitochondrial complex III, thereby increasing the efficacy of radiotherapy [371].

Antifungal agents also play an important role in drug repositioning strategies for the treatment of various tumors [372–374]. Itraconazole is among the most well-studied broad spectrum antifungal agents for cancer treatment [374–378]. It has been reported that itraconazole can interact with mitochondrial protein VDAC1 and modulate the AMPK/mTOR signaling axis [379, 380]. Another study has demonstrated that itraconazole elicited apoptosis by altering MMP, reducing Bcl-2 expression and elevating caspase-3 activity [381]. Our group previously found that ketoconazole, a P450 inhibitor traditionally used for antifungal treatment [382], elicited PINK1/Parkin-mediated mitophagy and apoptosis, thereby suppressing HCC growth alone or synergistically with sorafenib [383]. In addition, Econazole (Eco), a potent agent used for tackling superficial mycosis, is now well recognized as an antagonist for store-operated Ca^{2+} channels to induce cell death of leukemia [384–386]. Expectedly, it has now been shown to trigger mitochondrial-mediated apoptosis and cause cytochrome c leakage and apoptosis-inducing factor (AIF) translocation [387].

In conclusion, repurposing of broadly antimicrobial compounds emerges as an important strategy to provide complementary and alternative first-line drugs for effectively targeting mitochondria in cancer cells. We believe that repositioning antimicrobial agents will be an important topic in realizing the reversion of cancer drug resistance by eliciting mitochondria-dependent apoptosis.

Repositioning anti-cardiovascular disease drugs

Anti-cardiovascular disease drugs are another class of compounds that have attracted interest for their anticancer efficacy. An example is prazosin, an orally active postsynaptic selective alpha 1-adrenoreceptor antagonist used in treating hypertension, congestive heart failure (CHF), and even posttraumatic stress disorder (PTSD). It has been recognized to possess anticancer activity in some types of cancer by modulating the PI3K/Akt/mTOR signaling pathway [388]. Further, prazosin was demonstrated to intensify docetaxel-induced toxicity in prostate cancer cells [389]. In addition, another study demonstrated that prazosin triggers mitochondria-mediated

caspase executing apoptotic pathways in PC-3 cells, thus significantly reducing tumor mass in PC-3-derived cancer xenografts [390]. Quercetin, a bioflavonoid with multiple activities including antihypertensive, and anti-inflammatory, has been repurposed for cancer treatment [391–393]. Accumulating studies have been devoted to exploring the molecular basis underlying the antitumor efficacy of quercetin. The decrease in MMP and subsequent apoptosis represent potential mechanisms [394–396]. Another antihypertensive drug, lercanidipine, was shown to induce apoptosis accompanied by severe vacuolation derived from the ER and mitochondria, thereby enhancing the cytotoxicity of various proteasome inhibitors, including bortezomib, carfilzomib, and ixazomib, in many solid tumor cells [397]. Furthermore, a widely used and safe antihypertensive drug, telmisartan, was suggested to alter cell bioenergetics by triggering mitochondrial fission and ROS accumulation, thereby sensitizing melanoma cells to treatment with vemurafenib [398].

Taken together, anti-cardiovascular disease drugs hold great potential to be endowed with novel characteristics to tackle tumors in a mitochondria-dependent way.

Repositioning antidepressant drugs and anti-neurodegenerative drugs

It has been increasingly recognized that antidepressant drugs exert anti-neoplastic properties, in addition to their well-documented ability to modulate neurotransmission [399–402]. Tricyclic antidepressants and their analogs are among the most well-studied repurposed drugs for cancer therapy. They have exhibited excellent efficacy in halting cancer cell growth and metastasis [403–406]. Interestingly, the antitumor efficacy of imipramine and amitriptyline primarily relies on their metabolic modulating ability in restoring the proper function of mitochondria, which differs from those functioning through disturbing mitochondria [407]. For instance, recent investigations showed that imipramine and amitriptyline restore stressed mitochondria and stimulate their function to hijack the aggressive character of cancer caused by mitochondrial dysfunction [408]. Chlorimipramine, another tricyclic antidepressant, has been shown to specifically inhibit mitochondrial CIII and cause decreased MMP as well as mitochondrial swelling and vacuolation, thus exhibiting a selective antitumor effect [409]. In addition, fluoxetine has been reported to increase doxorubicin accumulation within multiple drug-resistant (MDR) cells and inhibit drug efflux both in vivo and in vitro in resistant tumor models [410]. It is also able to induce mitochondria-mediated cell death in human epithelial ovarian cancer [411, 412]. Moreover, nortriptyline can induce both Fas, FasL, FADD axis-mediated extrinsic apoptosis and mitochondria dysfunction-triggered intrinsic apoptosis, thus suppressing bladder tumor growth in vivo [413].

Agents for treating neurodegenerative disease (such as Alzheimer's and Epilepsy) have also been observed to be efficacious in the prevention and treatment of tumors [414, 415]. Valproic acid (VPA), an antiepileptic drug, has been shown to inhibit class I HDAC and exert antiproliferative, pro-apoptotic, and chemo-sensitizing effects in human lung cancer and colorectal cancer by restraining the cell cycle and eliciting ROS generation [416, 417]. In addition, VPA significantly induced mitochondrial dysfunction, thus reducing respiration and ATP production causing mitochondria-dependent apoptosis, which potentiated TRAIL-mediated cytotoxicity on cultured thoracic cancer and HCC cells [418, 419].

Repositioning anti-inflammatory and antirheumatic drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., indomethacin, ibuprofen, aspirin, and diclofenac) are the most commonly prescribed compounds for treating pain and inflammation [420–422]. It is widely accepted that NSAIDs possess anti-neoplastic effects in a wide spectrum of cancers [423–426]. In fact, prolonged NSAID administration reduces the risk of developing tumors [427, 428], and these non-oncology drugs are now applied to combination therapeutic regimens to potentiate the efficacy of chemotherapy and radiotherapy [429]. Based on the inhibitory effect on prostaglandin-synthesizing cyclooxygenases 1 and 2 (COX-1/2) and the role of nonsteroidal anti-inflammatory drug-induced gene NAG-1 in initiating the intrinsic apoptosis pathway [430], the mechanism of action underlying their antitumor efficacy is strongly related to mitochondrial dysfunction and ROS production caused by inhibition of mitochondrial respiration [431, 432]. This is best exemplified by aspirin, an FDA-approved NSAID for the treatment of pain and fever [433, 434]. Studies focusing on its antitumor mechanisms revealed that aspirin causes cytochrome c leakage and induces caspase-dependent apoptosis in cancer cells [435]. This mitochondrial damage is also probably responsible for the circumvention of resistance and sensitization to cisplatin by asplatin, a Pt(iv) prodrug of cisplatin, due to the ligation of aspirin [436]. Indomethacin, another NSAID initially used for treating rheumatic disease, has been found to induce mitochondria-mediated apoptosis in doxorubicin-resistant lung cancer cells through an MRP1-dependent mechanism [437]. In addition, indomethacin can activate the PKCζ-p38-DRP1 pathway to impair mitochondrial dynamics, thus inducing apoptosis in gastric cancer [438].

Other groups of anti-inflammatory and/or antirheumatic drugs also exhibit antitumor efficacy. Auranofin, an inhibitor of thioredoxin reductase (TrxR) initially

developed for the treatment of rheumatoid arthritis, exhibited anticancer activity against various tumor types. It was approved for clinical trials in lung and ovarian carcinomas [439–443]. Further investigations revealed that auranofin targets both the cytosolic and mitochondrial forms of TrxR, indicating that mitochondrial alterations might participate in the inhibitory effect of auranofin on cancer [444, 445]. In addition, Euphorbia formosana Hayata (EF), a Taiwanese medicinal plant for the treatment of rheumatism, has been repurposed for tumor suppression by eliciting apoptosis via the Fas and mitochondrial pathways in leukemic cells [446].

In summary, anti-inflammatory agents, pain-relieving medication, and antirheumatic drugs are now documented to be effective again diverse critical disorders including cancer, for which mitochondrial-related mechanisms are well recognized to be involved in their antitumor effects.

Repositioning ion chelating agents

Ion chelating agents represent a category of effective antitumor agents by targeting mitochondria, as mitochondria use metals (such as iron, copper, calcium, zinc) for the synthesis of cofactors of oxidation–reduction enzymes [447]. Deferiprone (DFP), an iron chelator used clinically in thalassemia, kidney disease, and Friedreich's ataxia, has been identified to reduce the proliferation and migration of cancer cells [448, 449]. The underlying mechanisms are well documented to involve the suppression of mitochondrial metabolism and the respiration rate, as well as induction of ROS production [450, 451]. VLX600, a recently designed iron chelator, has been characterized as a mitochondrial OXPHOS inhibitor which exhibited outstanding antitumor ability ovarian and breast and colorectal cancers [452–454]. Intriguingly, VLX600 was reported to inhibit mitochondrial respiration and augment the efficacy of imatinib in gastrointestinal stromal tumors [455]. It has also been suggested to sensitize ovarian cancer cells to platinum agents and PARPis (two standard-of-care therapies) [456].

Another metal with important functions in cancer progression is copper. Tetrathiomolybdate, a copper-chelating drug used in the treatment of copper overload disorder, has also shown obvious antitumor effects. Besides reducing angiogenesis, it can impair mitochondrial respiration as well as ATP production mainly by inhibiting copper-dependent mitochondrial C IV activity [457, 458]. In recent decades, disulfiram, the alcohol-aversion drug which functions in a copper complex to treat alcohol abuse [459], has attracted considerable attention for its alone or synergetic anticancer activity [460–465]. It functions as a disulfiram-Cu^{2+} complex (DSF-Cu^{+}/Cu^{2+}) to induce mitochondrial fission and reduce MMP, thus suppressing tumors via a redox-related apoptosis process [466]. In addition, elesclomol exerts potent anticancer activity by inducing oxidative stress and apoptosis [467–471]. Mechanistically, elesclomol forms an elesclomol-Cu (II) complex by chelating copper (Cu) outside of cells, which rapidly transports copper into the mitochondria, thus inducing mitochondrial ROS accumulation [472, 473]. Other types of metal chelators, including zinc and calcium chelating agents, have also been recognized as effective antitumor agents [474, 475].

Additionally, there are other compounds that do not belong to the groups discussed above which could be repositioned for cancer therapy via mitochondrial-mediated mechanisms. For instance, besides the palliative effects, cannabinoids and their analogs have shown promise as antitumor agents to reduce proliferation, induce apoptosis and autophagy, inhibit invasion and angiogenesis, and improve chemosensitivity to anticancer drugs [476]. Unequivocally, cannabinoids have been demonstrated to disrupt mitochondria damage and trigger ROS production both in human primary tumors and those resistant to chemotherapeutic drugs [477–479]. Furthermore, many commonly used chemotherapeutic drugs have been proven to interfere with mitochondria to promote anticancer effects, including, but not limited to, cisplatin [480, 481], doxorubicin [482, 483], sorafenib [484], and tamoxifen [485]. This broad variety of agents provide a plethora of options for tumor therapy by targeting mitochondria. We believe that targeted delivery of these drugs to mitochondria could benefit cancer treatment and overcome drug resistance.

In summary, repurposing non-oncology drugs is considered as an effective strategy to alleviate the current lack of mitochondria-targeting drugs. It holds the potential to develop effective agents in a short time period with lower development costs. However, it is not trivial to successfully apply suitable non-oncology drugs as anticancer therapeutics. Assessment of their effectiveness and understanding the underlying mechanistic in preclinical models are critical.

Mitochondria-targeted drug delivery system and multifunctional strategy

In recent years, organelle-specific delivery of bioactive molecules has been widely utilized for cancer treatment to achieve high selectivity, maximum therapeutic effects, minimum side effects, and minor resistance [486–490]. Mitochondria-targeting therapeutic strategies can directly affect the mitochondrial membrane or matrix, mitochondrial metabolism, and the mitochondrial apoptosis or regulatory signaling pathways [306, 491–494]. Researchers have developed or identified a

number of mitochondria-targeted drug delivery systems (MTDDSs), with most of them currently transporting chemotherapeutics into the mitochondria based on the high membrane potential across the inner mitochondrial membrane or the mitochondrial protein import machinery [495–498]. The following section will provide insights into the application of novel mitochondria-targeting strategies for cancer therapy (Table 4).

Mitochondrial protein import machinery-based targeting strategies

Except for a small number of mitochondria-encoded factors (e.g., key proteins in the ETC, rRNAs, tRNAs), the vast majority of proteins present in the mitochondria are encoded by the nucleus and translocated from the cytosol [499–503]. Transporting machinery protein complexes (e.g., TIM/TOM complex) recognize and transport these proteins from the cytoplasm to the mitochondria, where proteins with mitochondria-targeting signal peptides (MTSs) are escorted from the cytosol to mitochondrial outer membrane [504, 505]. MTSs always exhibit positive charge and easily form amphiphilic α-helices and thus have been successfully used for the selective and effective delivery of therapeutics to mitochondria for disease treatment, including cancer therapy [506]. In addition, MTSs conjugate to, and deliver, a variety of cargo molecules (e.g., proteins, nucleic acids). For instance, p53-BakMTS/p53-Bax were synthesized via fusing p53 or its DNA-binding domain (DBD) to MTSs from Bak or Bax by Matissek et al. This regiment is capable of targeting p53 to the mitochondria and executing mitochondria-mediated apoptosis in cancers [507]. Several mitochondria-targeting units take advantage of the IMM-embedded transporters. For example, a self-assembled protein nanoparticle named GST-MT-3(Co^{2+}) NPs was prepared by Zhu et al., via covalently conjugating paclitaxel to GST-MT-3(Co^{2+}), to specifically target mitochondria. Co^{2+} in the NPs depolarized the MMP and elevated ROS, which subsequently induced apoptosis to execute antitumor effects. Intriguingly, this nanoparticle exhibited a synergistic effect manifesting as 50-fold lower paclitaxel dosage which possessed a highly effective antitumor effect [508]. Similarly, a functional hybrid peptide (MTS-R8H3) was used to prepare a modified targeted liposome, DOX/CEL-MTS-R8H3 lipo, for codelivery of doxorubicin hydrochloride (DOX) and celecoxib (CEL) [509]. This liposome codelivery system exhibited remarkable treatment efficacy on killing DOX-resistant MCF-7 (MCF-7/ADR) cells, providing a promising strategy for overcoming drug resistance in breast cancer.

Cell-penetrating peptide-based mitochondria-targeting strategies

Cell-penetrating peptides (CPPs) are nontoxic, short, cationic, and/or amphipathic peptides able to directly cross the cellular membrane [510–512]. They serve as a popular and efficient vector for delivering a broad variety of cargoes, including oligonucleotides, proteins, and therapeutics [513–515]. Many efforts are being made to improve their cell specificity for selective uptake by tumor cells, permitting medical applications [516–518]. Modifying the CPPs according to microenvironment condition is a widely used strategy. Particularly, mitochondria-penetrating peptides (MPPs) have been developed to deliver a variety of antitumor cargoes into mitochondria, which can inhibit tumor growth in vivo and in vitro [519–522]. For example, Dox was intercalated into the Cyt c aptamer contained DNA duplex and subsequently loaded in the dendrigraftpoly-L-lysines (DGL) and combine to cyclopeptide RA-V contained pH-sensitive liposomal shells, for preparing a MPP-modified DGLipo NPs. This system could successively deliver both DOX and RA-V into lysosome and mitochondria of cancer cells, and achieved a spatiotemporally controlled release of them to monitor cytochrome c release and apoptotic process, leading to enhanced therapeutic outcomes in MDR tumors [462]. In addition, the TAT-PEG-DOPE system (methoxy (polyethylene glycol)-2000–1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine (mPEG-DOPE) and transactivator of transcription (TAT) peptide conjugated PEG-DOPE) is an example, in which sulfonamide will lose charge and detach when it suffers a decrease in pH, so that exposed TAT can interact and take the drug-loaded micelles to selectively kill tumor cells [523]. Several other novel CPPs for targeting cancer cell mitochondria, including Pal-pHK-pKV, an engineered peptide performed with the N-terminus of the HK-II protein [524]; pHK-PAS, achieved by covalently coupling N-terminal 15 aa of HKII (pHK) to a short, penetration-accelerating sequence (PAS) [525]; MTP3, another engineered peptide synthesized via resin-based solid-phase peptide synthesis, are also serving as efficient tools to deliver exogenous therapeutics into mitochondria and representing promising strategy in cancer therapy.

Delocalized lipophilic cation (DLC)-based mitochondria-targeting strategies

It has been well demonstrated that the MMPs of tumor cells are usually higher than that of non-malignant cells [526–528]. The hydrophobic surface areas and delocalized positive charge of DLCs permit them to rapidly pass through membrane bilayers and accumulate in cancer cells because of the more negative MMPs in cancer cells [529–532]. This offers a selective drug delivery approach

Table 4 Representative mitochondria-targeting therapeutic regimens

Mitochondria-targeted machinery	Mitochondria-targeted delivery method	Therapeutic regimens	Molecular mechanisms	Effects on cancer	Ref
Mitochondrial protein import machinery	Mitochondria-targeting signal peptides	M-ChiP	ROS production	Necrosis, enhanced therapeutic effect with reduced side effect	[580]
		AuNR@MSN-ICG-β-CD/Ada-RLA/CS (DMA)-PEG	ROS production; local hyperthermia	Enhanced antitumor effect with minimal side effect	[581]
		p53-BakMTS (or BaxMTS) and DBD-BakMTS (or BaxMTS)	Activation of MOMP and caspase-9	Apoptosis	[507]
		DOX/CEL-MTS-R8H3	ROS production; inhibition of P-gp efflux activity	Overcoming drug resistance in breast cancer	[509]
	Protein nanoparticle	GST-MT-3(Co^{2+}) NPs	ROS production; reduction of MMPs	Suppressing tumors and prolonging survival	[508]
Cell-penetrating peptide-based	Cell-penetrating peptide	Pal-pHK-pKV	Targeting the VDAC1-hexokinase-II complex	Amplifying lung cancer cell death	[524]
		DGLipo NPs	ROS production	Overcoming multidrug resistance	[582]
		TAT-PEG-DOPE system	/	Selectively killing tumor cells	[523]
		pHK-PAS	Cytochrome c release; disruption of the mitochondria-HKII association	Apoptosis	[525]
	MTP3	Mitochondrion-targeting prodrug (compound 17, doxorubicin-based prodrug)	Mitochondrial depolarization	Enhanced cytotoxicity against human tumor cells while negligible toxicity toward normal cells	[583]
Delocalized lipophilic cation (DLC)-based	Triphenylphosphonium (TPP)	TPP-LND-DOX NPs	Apoptosis	Conquering drug resistance	[243]
		TPP-PEG-L	Apoptosis	Enhancing paclitaxel-induced cytotoxicity and antitumor efficacy	[540]
		TPGS1000-TPP-Targeting paclitaxel liposomes	Apoptosis	Inhibiting drug-resistant lung cancer	[541]
		THMSNs@LMDI	Singlet oxygen generation	Sensitizing A549/MCF-7 cells to doxorubicin	[578]
		Fe3O4@Dex/TPP/PpIX/ss-mPEG	Fenton reaction	Improving antitumor therapeutic efficacy	[574]
		TPP-PF127-HA	Cytochrome c release; activation of caspase-3 and caspase-9	Eradicating drug-resistant of lung cancer	[497]
		Targeted Sunitinib Liposomes and Targeted Vinorelbine Liposomes	Activation of caspase-9 and caspase-3	Treating invasive breast cancer	[584]
	Dequalinium (DQA)	DQA-PEG2000-DSPE	Apoptosis	Enhancing the anticancer efficacy against cisplatin-resistant A549 cells	[545]
		DQA and folate-loaded functional DOX nanoparticles	Activation of caspase-9 and caspase-3 cascade	Overcoming multidrug-resistant cancers	[546]
	Metal complexes	Ir-photoacid generator (PAG)	$^1O_2$ generation	Killing cancer cells effectively even under hypoxic conditions	[585]
	Guanidinium	BZP, TPY, PPY, THPY	ROS elevation	Against cisplatin-resistant A549 cells	[586]

Table 4 (continued)

Mitochondria-targeted machinery	Mitochondria-targeted delivery method	Therapeutic regimens	Molecular mechanisms	Effects on cancer	Ref
Synthetic secretion system in *E. coli*	T3SS	enT3SS	Cytotoxic activity	Eliminating tumors and reducing the mortality of tumor-bearing animals	[553]
Others	Coumarin	Bromocoumarin platinum 1	p53 apoptosis pathway	Overcoming cisplatin resistance	[556]
		ZIF-90@DDP	/	Overcoming platinum-resistant ovarian cancer	[557]
	Berberine (BBR)	Paclitaxel (PTX)-ss-BBR	ROS production; G2/M arrest	Enhancing the effect of CT in A549 cells	[587]
	d-(KLAKLAK)2	d-(KLAKLAK)2	Cytochrome c release	Enhancing the anticancer efficacy	[588]
	Ion-pair stabilized lipid matrix	Bio-nFeR	Apoptosis; Modulation of lipid metabolism	Enhanced bioavailability; Against multiple cancer stem cells	[589]
Enzymatic self-assembly	Enzymatic cleavage of branched peptides	Flag-(C16)2- CLRP	Inhibition of the mitochondrial protein synthesis; Cytochrome c release	Sensitizing cancer cells to cisplatin	[319, 590]

to deliver compounds to tumors with little toxicity to normal healthy cells.

While Rhodamin123 was the first DLC identified to markedly inhibit the growth of carcinoma cell lines and prolong the survival of tumor-bearing mice [533, 534], the triphenylphosphonium (TPP) cation is the most well-documented DLC that has been used for mitochondria targeting [346, 495, 535]. TPP^+ cations were conjugated to a wide variety of synthesized residues and incorporated into the liposomal lipid bilayer to make drug delivery systems for mitochondria targeting and tumor suppression [536–539]. For example, Biswas et al. synthesized a polyethylene glycol-phosphatidylethanolamine (PEG-PE) and TPP^+ group modified liposomes (TPP-PEG-L). TPP-PEG-L has been demonstrated to enhance paclitaxel-induced cytotoxicity and antitumor efficacy compared to plain liposomes (PL) from efficient mitochondria targeting [540]. In addition, a D-α-tocopheryl polyethylene glycol-1000 succinate-triphenylphosphine (TPGS1000-TPP) was incorporated onto the surface of paclitaxel liposomes to prepare TPGS1000-TPP conjugate. This regiment could selectively accumulate into the mitochondria and initiate caspase-9- and caspase-3-mediated apoptosis, thereby exhibiting significant anticancer efficacy in drug-resistant A549/cDDP xenograft and cells [541].

Dequalinium chloride (DQA) has been regarded as a new class of anti-carcinoma agents based on its selective localization and accumulation within the mitochondria of cancer cells [542–544]. For example, a dequalinium polyethylene glycol-distearoylphosphatidyl-dylethanolamine (DQA-PEG2000-DSPE) conjugate was synthesized to develop mitochondrial-targeted resveratrol liposomes to overcome drug resistance. This mitochondrial-targeted liposome is significantly accumulated in the mitochondria and induces apoptosis in both nonresistant and resistant cancer cells by dissipating MMPs. In addition, cotreating this liposome with vinorelbine liposomes remarkably enhanced the anticancer efficacy against cisplatin-resistant A549 cells [545]. Furthermore, functional nanoparticles based on DQA were developed for targeted delivery of classical cytotoxic anticancer drugs (such as doxorubicin) to tumor cells, which showed significant anticancer efficacy in a drug-resistant tumor model via triggering cytochrome c release and mitochondrial apoptosis [546].

Newly developed mitochondria-targeting units-based strategies

In recent years, numerous drug delivery systems, including liposomes, micelles, "smart" polymers, and hydrogels, have been developed for cancer therapy [547–552]. For instance, to achieve accurate delivery to mitochondria with high specificity and low size, a native genetic system encoded in *Salmonella* pathogenicity island-1 (SPI-1) was used by Lim et al. [553]. In their study, *E. coli* carrying synthetic T3SS and MTD on plasmids could eliminate tumors and reduce the mortality of tumor-bearing animals. Furthermore, another study developed a peri-mitochondrial enzymatic self-assembly system to deliver chloramphenicol (CLRP) to the mitochondria in cancer cells. Importantly, their results suggested that this new system could overcome cisplatin resistance by inhibiting the synthesis of mitochondrial proteins.

Modifying traditional drugs with newly developed mitochondria-targeting units also exhibited potential to reduce side effects and reverse drug resistance to some extent [554, 555]. For instance, Ma et al. designed bromocoumarin platinum 1 therapeutic (a coumarin-Pt (IV) prodrug) to simultaneously target mitochondria and nuclei [556]. This therapy allows simultaneous accumulation of high concentrations of Pt in both the nDNA and mtDNA, thus triggering apoptosis to overcome cisplatin resistance. Moreover, p53 activation promoted Pt–DNA-induced apoptosis in cancer cells, leading to obvious anticancer activity with this prodrug. In addition, Xing and co-workers synthesized a mitochondria-targeting zeolitic imidazole framework loaded with platinum (ZIF-90@DDP) to kill cancer cells by promoting effective drug release under specific pH and ATP levels, thus providing a new strategy for reversing platinum resistance in ovarian cancer [557].

Multifunctional drug delivery strategies

At present, mitochondria-targeting photothermal therapy (PTT), photodynamic therapy (PDT), chemodynamic therapy (CDT), and related combinational therapies have attracted global attention due to their advantages of a wide therapeutic range, minimal toxicity, excellent safety profile, noninvasiveness, and low drug resistance [558–560]. PTT triggers thermal damage by conversing light energy into heat to kill cancer cells [561–563]. In recent years, a variety of photothermal materials, including inorganic nanomaterials (such as gold nanocages, gold nanorods, and other gold nanostructures), transition metal sulfide or oxide nanoparticles, have been developed to improve the energy conversion from near infrared (NIR) light [564, 565]. As such, PTT has shown remarkable achievements in the treatment of various tumors [566–569]. PDT is available for treating a broad variety of cancers through local ROS production only in the light-exposed region by utilizing photosensitizer (PS), light, and oxygen [570–573]. Recently, Fe_3O_4@Dex-TPP nanoparticles have been prepared by coprecipitation in TPP-grafted dextran (Dex-TPP) and Fe^{2+}/Fe^{3+} and then incorporated with the photosensitizers of

protoporphyrin IX (PpIX) and glutathione-responsive mPEG-ss-COOH to form a fenton reaction-assisted PDT, noted Fe_3O_4@Dex/TPP/PpIX/ss-mPEG nanoparticles [574]. This nanoparticle targets mitochondria by photoinduced internalization, leading to ROS generation and the fenton reaction-produced O_2, thus significantly improving the therapeutic efficacy on tumor. In addition, Zeng et al. synthesized bifunctional nanoprobe (FA-NPs-DOX) by loading DOX to NaYF4:Yb/Tm-TiO2 inorganic photosensitizers for in vivo inorganic PDT [575]. In this study, folic acid (FA) targeting and NIR-triggered inorganic PDT accelerated the release of DOX and promoted the inhibition rate in drug-sensitive MCF-7 and resistant MCF-7/ADR cells.

In addition, other therapies, including CDT [576, 577], sonodynamic therapy (SDT), gas therapy, radiation therapy (RDT), alone or in combination with other treatments targeting mitochondria to inhibit tumors, are emerging, as described in a comprehensive review [491]. For instance, Shi et al. designed a mitochondria-targeted hollow mesoporous silica nanoparticles (THMSNs) loaded with L-menthol (LM) to carry DOX and NIR dye indocyanine green (ICG), named THMSNs@LMDI [578]. Under NIR irradiation, this system simultaneously produces photodynamic and photothermal therapy effect via DOX release and apoptosis activation, thereby sensitizing A549/MCF-7 cells to DOX. Intriguingly, a specific targeting of mitochondria and imaging-guided chemo-photothermal therapy against cisplatin resistance was proposed by Yang and colleagues [579]. In this work, Pt (IV)-NPs, a nanoparticle precisely assembled by biotin-labeled Pt (IV) prodrug derivative and cyclodextrin-functionalized IR780, integrated with targeting units, imaging moieties into a single regiment to overcome and even completely eliminate cisplatin resistance A549R tumors, thus providing a beneficial precise therapeutic. Undoubtedly, combination therapies achieve synergistic effect of anticancer and hold more beneficial for future clinical translation.

In summary, the development of mitochondria-targeting units and combinational strategies for cancer therapy has achieved precise treatment at lower drug doses (Table 4), offering excellent prospects for improving the therapeutic effect and overcoming drug resistance.

Therapeutic applications of mitochondrial transplantation

The transplantation of mitochondria from healthy cells to abnormal cells has emerged as a novel and attractive therapeutic strategy to treat diseases caused by mitochondria damage or dysfunction [591–595]. While intercellular mitochondrial transfer functions as essential stress-adaptive mechanism to endow cancer cells with resistance to chemotherapy [175, 176], mitochondrial transplantation (mtTP) has been used in preclinical and clinical studies to restore mitochondrial function for cancer therapy and eliminate drug resistance [596–599]. For example, Chang et al. transferred mitochondria into breast cancer cell lines [321]. The results suggested that mitochondria transplantation-induced cell apoptosis inhibited cell growth and decreased oxidative stress, thereby increasing the susceptibility of both MCF-7 and MDA-MB-231 breast cancer cells to doxorubicin and paclitaxel. In addition, intercellular endocytosis (e.g., mitochondria internalization) was suggested to enhance the TCA cycle and aerobic respiration, attenuate glycolysis, and reactivate the mitochondrial apoptotic pathway, thereby inhibiting malignant proliferation and enhancing the radiosensitivity of gliomas in vitro and in vivo [600].

Overall, mtTP appears to be a very promising therapeutic option to fine-tune mitochondria function in cancer cells so that drug resistance might be overcome. However, research on mitochondrial transplantation for cancer treatment is still in its infancy. Further investigations including preclinical and clinical studies are required to determine if it is effective in sensitizing cancer cells to radio- or chemotherapy. Additionally, various technical and ethical issues need to be addressed before its actual clinical application.

Conclusions and perspectives

Mitochondria are crucial players in cancer cell survival, as they are the bioenergetic and biosynthetic hub that coordinates cellular respiration, FAO, the TCA cycle, ETC, Ca^{2+} signaling, and redox homeostasis. Cancer drug resistance, as an adaptive strategy employed by cancer cells to survive stress conditions, is inevitably associated with mitochondrial-related pathways [62, 82, 601]. In fact, emerging evidence strongly indicates that resistant tumor cells exhibit high mitochondrial respiration and OXPHOS status [602, 603]. Therefore, targeting mitochondria represents a promising cancer treatment avenue and chemoresistance overcoming strategy. In this review, we have elaborated on the mechanisms of mitochondrial dynamics in number, structure, and location to maintaining mitochondrial function to endow cancer cells with metabolic flexibility for adapting to stress conditions, with an emphasis on their regulatory role in drug resistance. We have also summarized recent advances that focus on developing therapeutics that specifically target the mitochondria for cancer therapy. Notably, two representative compounds, metformin and CPI-613, have been taken on to phase III clinical trials (Table 2). Lastly, we have highlighted the repurposing of "old" drugs for mitochondria targeting in tumor therapy with the potential to effectively kill tumors. The development of mitochondria-targeting approaches will undisputedly

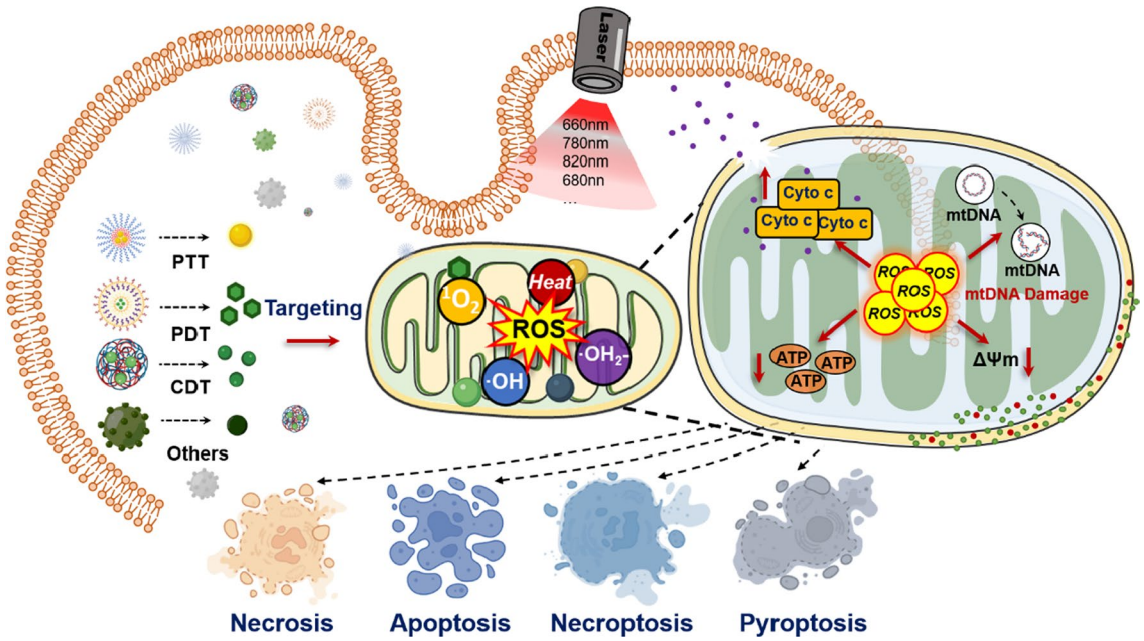

Fig. 4 Schematic illustration of the mitochondria-targeting strategies and their anticancer effect. Integrated therapeutics include, but are not limited to, PTT, PDT, and CDT. Their function requires the rational design, functionalization, and application of diverse mitochondria-targeting units, such as organic phosphine/sulfur salts, QA salts, transition metal complexes, and MTPs. The generation of superoxide ($\cdot O_2^-$), singlet oxygen ($^1O_2$), ·OH or heat results in mitochondrial damage, thus inhibiting energy supply and triggering cancer cells death

boost the precision of cancer treatment at lower drug doses (Fig. 4, Table 5).

It is worth noting that further investigations are urgently needed to handle several key mitochondrial-related questions for their successful application in clinic cancer treatment. First, it will be pivotal to identify additional molecular mechanisms that cause the high OXPHOS status of cancer cells. It is also important to explore the roles and mechanisms of metabolic advantages in maintaining this high OXPHOS activity and how they modulate resistance to targeted or chemotherapies, as mitochondria are the hub of many metabolic pathways. Second, the roles of mitochondrial reshaping, rebuilding, and recycling are largely in a context-dependent manner, which remain vastly unexplored. Further study focusing on developing rational targeted approaches to modulate adaptive response will definitely require the possibility to accurately map dynamic processes and monitor bioenergetic and metabolic changes over a considerable time period [621]. Theoretically, drug repurposing and systematic screening approaches as well as advanced bioinformatics could replenish the inventory of antitumor drugs and break one of the current bottlenecks of drug development. However, it is important to decipher their mechanism of action and identify patients who would benefit from treatment with these compounds. In addition, more preclinical studies and clinical trials must be completed before such interventions become common practice in cancer therapy.

Modification of traditional therapeutics with mitochondria-targeting units has potential for reducing drug resistance and adverse side effects. Many of these strategies have been applied as preclinical or clinical antitumor therapies. However, safety evaluation based on biocompatibilities, release, accumulation, and metabolism is a prerequisite for their application. Indeed, limitations in the materials, such as toxicities and poor drug loadings, have restricted the further application of multifunctional nanodrugs. Future pharmaceutical research should focus on addressing the aspects mentioned above while exploring new materials. Notably, these therapeutics need to overcome both physiological and biological barriers before localizing to their target sites to take effect. What happens in these processes will affect the release of drugs and affect their antitumor efficacy. Therefore, it is important to endow the delivery system with some specific related functions. In addition to structural reformation, future research needs to investigate the mechanisms of exerting treatment, especially at the molecular level.

In the coming years, we predict that advances in omics technology, PET imaging combined with cancer genomics, will help a timely elucidation of metabolic

Table 5 Overview of mitochondria-targeting strategies for cancer treatment

Mitochondria-targeting strategies	Description	Compositions	Characteristics	Refs.
Conventional chemotherapy	A promising strategy that directly acts on mitochondria to produce toxic substances to cells and induces cancer cell death by endogenous chemical energy without the stimulation of external light sources	CT drugs (Betulinic Acid, Resveratrol, Dicerca-linium Chloride, Benzo-α-pyrone (coumarin), α-TOS, Organic Arsenicals)	Easy to penetrate mitochondrial membrane and target mitochondria due to high lipid solubility; high effectiveness of tumor treat-ment	[556, 604, 605]
Nanoplatform loaded with CT/RT drugs	CT/RT drugs are modified by mitochondria-targeting units or designed as nanoplatforms for cancer treatment	CT/RT drugs (Lonidamine, Paclitaxel, Doxoru-bicin, Cisplatin); mitochondria-targeting units	High effectiveness of tumor treatment	[557, 587, 606]
CDT	A burgeoning therapy through undergoing a fenton reaction or a fenton-like reaction, which reacts with excessive intracellular hydrogen peroxide (H_2O_2) in tumor tissues to generate hydroxyl radicals (·OH)	CT drugs; mitochondria-targeting units	Low invasiveness; consumption of endog-enous H_2O_2 without external energy; little normal tissue toxicity	[576, 577]
PTT	Killing cancer cells with thermal damage (conversion of light energy into heat) utilizing an external light source (usually near-infrared (NIR) light) and photothermal agent as heat-generating source; PTT has strong absorption characteristics for NIR	Photothermal materials, external light source; mitochondria-targeting unit	Deep penetration and minimal damage to surrounding healthy tissue; noninvasiveness; Minimal side effects; temporal and spatial selectivity	[567, 607, 608]
PDT	A locally targeted therapy utilizing a photo-sensitizer (PS), light, and oxygen to selectively kill tumors	PS, light, oxygen, serval lipophilic, and cati-onic groups	Accurate controllability; minimal drug resist-ance	[562, 570, 572]
RT-RDT	Stimulating PS to produce $^1O_2$ to kill tumors under ionizing radiation	PS, $^1O_2$, and mitochondria-targeting unit	Reach deeper tissues; low dosage possessing effective therapeutic effect	[609, 610]
SDT	To kill cancer cells by stimulating exogenous (ultrasound) to activate SDT agents for producing ROS, cavitation, air bubbles, and hyperthermia	Ultrasound, SDT agents, ROS, cavitation, air bubbles, and hyperthermia	Depth of tumor tissues can be realized by ultrasound; Achievement of noninvasive treatment; high precision of target lesion zones	[611]
Gene therapy	Replacement of defective genes by delivering wild-type ones into the host cell, or silencing a dominant mutant allele that is pathogenic to address mitochondrial diseases,	Therapeutic cargoes; delivery system	Precision treatment	[612–614]
Gas therapy	Using gaseous molecules to combat cancer	Gaseous molecules such as nitric oxide, CO, hydrogen sulfide, and hydrogen; mitochon-dria-targeting unit	Noninvasive in situ treatment with no depth limit	[615, 616]
Combination therapy	Combination of CT and PTT, CT and CDT, PDT and PTT, PDT and CDT; PDT and CT; PDT and Immunotherapy	/	Achieve synergistic effect of anticancer; minimize multidrug resistance; reduced pain in patients	[579, 617–620]

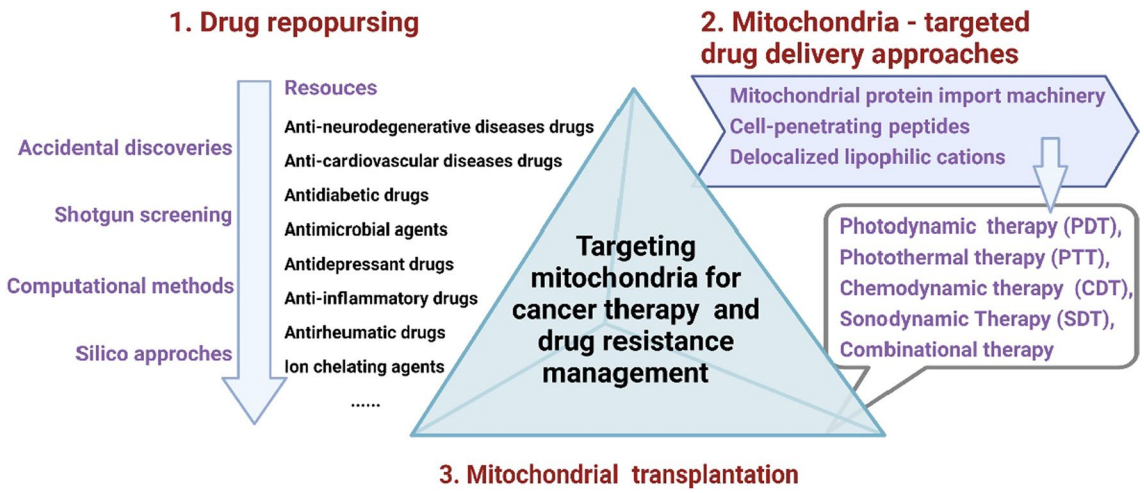

Fig. 5 Rational design for targeting mitochondria in cancer therapy. Drug repurposing, mitochondrial-targeted nanomedicines, and mitochondrial transplantation represent opportunity to offer promising strategies for targeting mitochondria to overcome cancer drug resistance. The mitochondrial inhibitors may be used in combination with chemotherapy, radiotherapy, or even immunotherapy to provide new avenues for cancer therapeutic regimes

vulnerabilities and lead to the recognition of rational combinations of mitochondria-targeting inhibitors with standard treatments, which will hopefully bring new and more effective strategies for cancer therapy and drug resistance management (Fig. 5) supporting precision/personalized medicine.

Abbreviations

2-DG: 2-Deoxyglucose; 3-BP: 3-Bromopyruvate; 5-fu: 5-Fluorouracil; α-TOS: Alpha-tocopheryl succinate; α-KG: α-Ketoglutarate; AOA: Aminooxyacetate; AML: Acute myeloid leukemia; α-KGDH: α-Ketoglutarate dehydrogenase; AIF: Apoptosis-inducing factor; AREs: Antioxidant response elements; AKT: RAC-alpha serine/threonine-protein kinase; BNIP3/NIX: Bcl2/adenovirus E1B 19 kDa interacting protein 3; BCL2L13: Bcl-2-like protein 13; BMSCs: Bone marrow stromal cells; Bz-423: 1:4-Benzodiazepine derivative; BITC: Benzyl isothiocyanate; CSCs: Cancer stem cells; CPPs: Cell-penetrating peptides; CDT: Chemodynamic therapy; CPT1/2: Carnitine palmitoyltransferase ½; CHF: Congestive heart failure; COX-1/2: Cyclooxygenases 1 and 2; CLRP: Chloramphenicol; DQA: Dequalinium chloride; Dox: Doxorubicin; DRP1: Dynein-related protein 1; DFP: Deferiprone; DCA: Dichloroacetate; DHODH: Dihydroorotate dehydrogenase; DIM: 3,30-Diindolylmethane; EGFR: Epidermal growth factor receptor; EVs: Extracellular vesicles; ETC: Electron transport chain; ER: Endoplasmic reticulum; ESCC: Esophageal squamous cell carcinoma; EF: Euphorbia formosana Hayata; FUNDC1: FUN14 domain-containing protein 1; FDX1: Ferredoxin 1; FIS1: Fission protein homologous protein 1; FAO: Fatty acid oxidation; FAs: Fatty acids; GCS: Glycine cleavage system; GLUT1: Glucose transporter 1; GLS: Glutaminase; GLUD1: Glutamate dehydrogenase 1; GOT2: Glutamate oxaloacetate transaminase 2; GPT2: Glutamate pyruvate transaminase 2; GSH: Glutathione; HK2: Hexokinase 2; HCC: Hepatocellular carcinoma; HDAC: Histone deacetylase; IMM: Inner mitochondrial membrane; IDH: Isocitrate dehydrogenase; LDH: Lactate dehydrogenase; MTHFD1: Methylenetetrahydrofolate dehydrogenase 1; MTHFD1 L: Methylenetetrahydrofolate dehydrogenase 1-like; MTHFD2: Methylenetetrahydrofolate dehydrogenase 2; MDR: Multiple drug-resistant; MTPs: Mitochondria-targeting peptides; MFN: Mitofusin; MCL1: Myeloid leukemia cell differentiation protein; MAM: Mitochondrial-associated endoplasmic reticulum membrane; MCUC: Mitochondrial Ca^{2+} uniporter complex; MSCs: Marrow stromal cells; MM: Multiple myeloma; MDPs: Mitochondrial-derived peptides; MCT1: Monocarboxylate transporter; MTDDSs: Mitochondria-targeted drug delivery systems; MTS: Mitochondria-targeting signal peptides; MPPs: Mitochondria-penetrating peptides; MPP+: 1-Methyl-4-phenylpyridinium; NSAIDs: Nonsteroidal anti-inflammatory drugs; NPs: Nanoparticles; NSCLC: Non-small cell lung cancer; NIR: Near infrared; OXPHOS: Oxidative phosphorylation; OMM: Outer mitochondrial membrane; OPA1: Optic atrophy 1; PFK: Phosphofructokinase; PEG-PE: Polyethylene glycol-phosphatidylethanolamine; PKM2: Pyruvate kinase isozymes M2; PPP: Pentose phosphate pathway; PGC1α: Peroxisome proliferator-activated receptorycoactivator-1; PL: Plain liposomes; PI3K: Phosphatidylinositol 3-kinase; PDT: Photodynamic therapy; PTT: Photothermal therapy; PDH: Pyruvate dehydrogenase; PTSD: Posttraumatic stress disorder; PDH: Pyruvate dehydrogenase; RDT: Radiation therapy; ROS: Reactive oxygen species; RIPK1: Receptor-interacting protein kinase 1; SHMT: Serine hydroxymethyltransferase; sORFs: Short open reading frames; SPI-1: Salmonella pathogenicity island-1; SDT: Sonodynamic therapy; TFAM: Transcription factor A, mitochondrial; TKI: Tyrosine kinase inhibitors; TCA cycle: Tricarboxylic acid cycle; TNTs: Tunneling nanotubes; TNBC: Triple-negative breast cancer; TPP: Methyltriphenylphosphonium; TAT: Transactivator of transcription; TrxR: Thioredoxin reductase; UPRmt: Unfolded protein stress response; VDAC1: Voltage-dependent anion-selective channel 1; VPA: Valproic acid; VDACs: Voltage-dependent anion-selective channel proteins; VK3: Vitamin K3.

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Author contributions

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