Review Article

Min Zhang, Yuchen Yang, Jiacheng Wu* and Qian Sun*

Multiple roles of mitochondria in tumorigenesis and treatment: from mechanistic insights to emerging therapeutic strategies

https://doi.org/10.1515/oncologie-2024-0596
Received November 14, 2024; accepted February 5, 2025;
published online March 18, 2025

Abstract: Mitochondria, the 'powerhouses' of cells, primarily produce ATP and also regulate homeostasis, apoptosis, and metabolism. In recent years, research advancements in oncology have highlighted the pivotal role of mitochondria in tumor initiation, progression, and therapeutic response. This review aims to provide a comprehensive summary of the latest research progress on mitochondrial functions in oncology, systematically discussing the mechanisms of mitochondrial dysfunction, metabolic reprogramming, and advances in mitochondrial-targeted therapies. Additionally, the complex role of mitochondria in tumor immunity is analyzed. Through integrated analysis and summary, this review seeks to reveal the significance of these findings in advancing basic cancer research and their potential implications for clinical applications, thereby offering new insights and directions for future cancer treatment strategies.

Keywords: mitochondria-targeted therapy; cancer therapy; nano-drug delivery systems; mitochondrial dysfunction; mitochondrial metabolism; tumor immunity

Introduction

Tumorigenesis is a complex process involving the activation of oncogenes, inactivation of tumor suppressor genes, dysregulation of apoptosis, and defects in DNA repair mechanisms [1–3]. As a critical organelle within cells, mitochondria are responsible not only for efficiently synthesizing ATP via the oxidative phosphorylation (OXPHOS) pathway to meet cellular energy demands [4], but also for deeply participating in the regulation of apoptosis, calcium ion homeostasis, reactive oxygen species (ROS) production, and the modulation of various signal transduction pathways [5, 6]. Notably, mitochondrial dysfunction has become a hallmark of cancer cells. In cancer cells, mitochondrial functions and metabolic states are significantly reprogrammed, influencing both their growth and proliferation dynamics and directly impacting their responsiveness to therapeutic interventions [7]. Thus, mitochondria have emerged as critical targets in cancer research and therapeutic fields. This review aims to thoroughly examine the multifaceted roles of mitochondria in tumorigenesis, progression, and therapeutic response, with an in-depth analysis of their mechanisms, providing insights for the development of novel and effective anti-cancer strategies.

Mitochondrial dysfunction and tumorigenesis

Mitochondrial DNA (mtDNA) mutations

Mutations in mitochondrial DNA (mtDNA) play a crucial role in tumorigenesis and progression (Figure 1) [8, 9]. As genetic material independent of nuclear DNA, mtDNA primarily encodes proteins involved in the OXPHOS process, which is essential for maintaining cellular energy metabolism and homeostasis [10, 11]. However, due to the lack of effective repair mechanisms and histone protection, mtDNA exhibits a mutation rate significantly higher than that of nuclear DNA, making it a prominent target in cancer research [12]. Through a detailed analysis of mtDNA mutations' role in cancer development, it has been found that these mutations promote tumor progression through various pathways.

***Corresponding authors: Jiacheng Wu**, Department of Urology, The First Affiliated Hospital of Soochow University, Suzhou 215006, China; and Department of Urology, Affiliated Tumor Hospital of Nantong University and Nantong Tumor Hospital, Nantong 226361, China, E-mail: 20234132078@stu.suda.edu.cn; and **Qian Sun**, Department of Medical Oncology, Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China, E-mail: sq_susan@163.com
Min Zhang, Department of Blood Transfusion, Zhongda Hospital, Medical School, Southeast University, Nanjing, China
Yuchen Yang, Department of Medical Oncology, Jinling Hospital, Medical School of Nanjing University, Nanjing, China

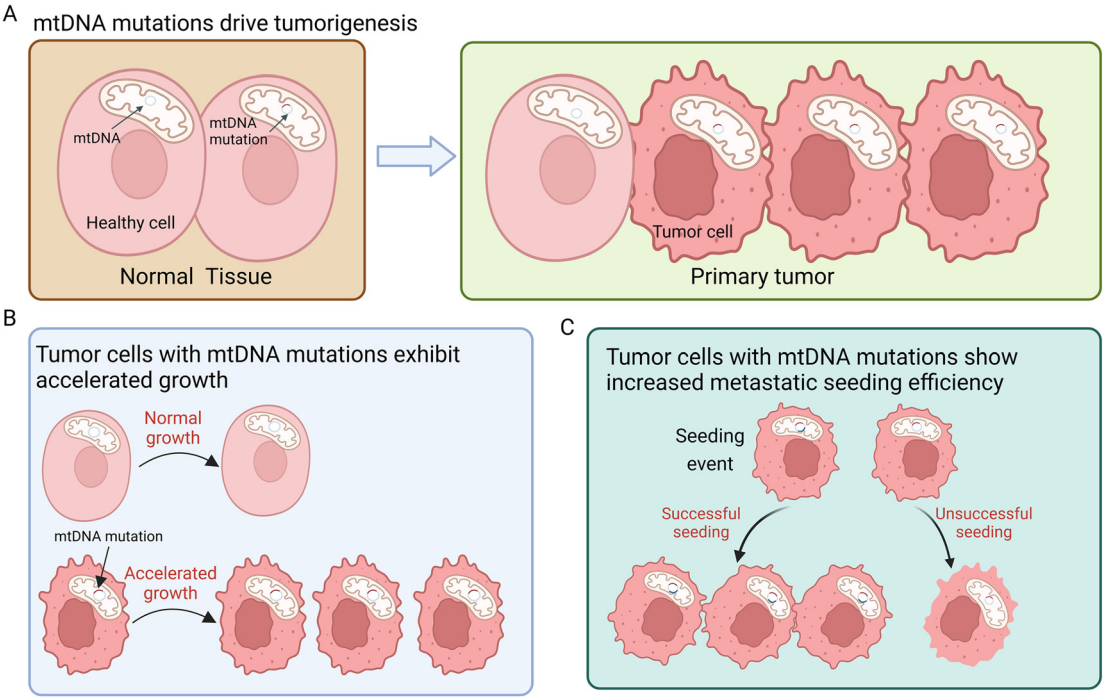

Figure 1: The role of mitochondrial DNA (mtDNA) mutations in tumorigenesis and metastasis [8]. (A) Mutations in mtDNA lead to the transformation of healthy cells into tumor cells, driving tumorigenesis and the formation of a primary tumor. (B) Tumor cells with mtDNA mutations exhibit enhanced metabolic adaptation, enabling accelerated growth compared to cells with normal mtDNA. (C) During metastatic progression, mtDNA-mutated tumor cells demonstrate an increased ability to undergo successful seeding at distant sites, while cells without the necessary adaptations experience unsuccessful seeding.

Firstly, mtDNA mutations can lead to mitochondrial respiratory chain dysfunction, affecting cellular energy metabolism and redox balance. This metabolic reprogramming not only provides the energy required for rapid tumor cell proliferation but also facilitates the formation of the tumor microenvironment (TME), enhancing the invasion and metastasis capabilities of tumor cells [13]. For instance, Smith et al. [14] demonstrated that mtDNA mutations leading to OXPHOS deficiencies are enriched in human adenoma-carcinoma sequences, potentially upregulating the *de novo* serine synthesis pathway (SSP) in response to OXPHOS deficiency, thereby enabling metabolic remodeling that confers a metabolic advantage to cancer cells. Secondly, mtDNA mutations can increase mitochondrial ROS production, further leading to the accumulation of DNA damage and gene mutations, creating a vicious cycle that continuously drives the malignant transformation of tumor cells [15]. This mechanism emphasizes the cumulative and amplifying effects of mtDNA mutations during tumorigenesis. For example, Li et al. [16] found that mtDNA heteroplasmic mutations underwent positive selection in the pathogenesis of breast cancer, causing shifts in the mitochondrial genetic landscape, which further supports this viewpoint. Additionally, mtDNA mutations finely regulate the growth and death balance of tumor cells by influencing processes like mitophagy and apoptosis [17]. This regulatory role allows tumor cells to survive and continue proliferating in adverse TME conditions, further exacerbating tumor malignancy. Abad et al. [18] demonstrated that mitochondria carrying mutated DNA contribute to the chemoresistance of triple-negative breast cancer cells through extracellular vesicle trafficking, further revealing mtDNA mutations' role in therapeutic resistance. Finally, mtDNA mutations can also influence the epigenetic state of tumor cells, further modulating the expression of tumor-related genes and promoting tumor progression [19].

In summary, mtDNA mutations play a central role in tumorigenesis and development by influencing energy metabolism, redox balance, ROS production, mitophagy, and apoptosis. Additionally, the close association of mtDNA mutations with various cancer types and their potential applications in cancer diagnosis and therapeutic resistance make mtDNA an attractive target in cancer research. Future studies should further explore the specific mechanisms of mtDNA mutations and their potential applications in cancer therapy to provide novel strategies and insights for cancer treatment.

Dysfunction of the mitochondrial respiratory chain

The mitochondrial respiratory chain comprises protein complexes (Complexes I to V) in the inner mitochondrial membrane Its primary function is to generate ATP through the OXPHOS process, providing energy for the cell. Under normal conditions, electrons are transferred from NADH and $FADH_2$ to oxygen, producing water and releasing energy, while the proton gradient drives ATP synthesis (Figure 2) [20]. However, in tumor cells, the mitochondrial respiratory chain complexes often suffer from dysfunction, leading to reduced OXPHOS efficiency and decreased ATP production [21]. One of the most direct consequences of mitochondrial respiratory chain dysfunction is the excessive generation of ROS. Normally, electrons are transferred through the respiratory chain complexes and ultimately reduced to water, but when the respiratory chain is impaired, some electrons leak to oxygen molecules, producing superoxide anions ($O_2^{\bullet-}$), which are converted into hydrogen peroxide (H_2O_2) and other forms of ROS [22–25]. The accumulation of ROS triggers oxidative stress, damaging intracellular DNA, proteins, and lipids, and activates signaling pathways (e.g., NF-κB, p53, and JNK), promoting tumor cell proliferation, survival, and metastasis [26, 27].

The loss of mitochondrial respiratory chain function also leads to the dissipation of the mitochondrial membrane potential, a process that is often closely associated with apoptosis. The normal mitochondrial membrane potential maintains the proton gradient required for ATP synthesis, but when the respiratory chain function is impaired, the imbalance of the membrane potential results in mitochondrial dysfunction [28]. This dysfunction promotes the release of pro-apoptotic factors, such as cytochrome *c* (Cytc), from the mitochondria into the cytoplasm, activating the caspase cascade [29]. However, tumor cells avoid programmed cell death by upregulating anti-apoptotic proteins such as B-cell lymphoma-2 (Bcl-2), which suppress apoptotic signals within the mitochondria [30]. This imbalance in apoptotic signaling allows tumor cells to survive under abnormal conditions, thus increasing the aggressiveness and drug resistance of tumors.

Drug resistance is a significant challenge in cancer therapy. Studies have shown that mitochondrial respiratory chain dysfunction is closely linked to the development of resistance. For example, in hepatocellular carcinoma, sorafenib induces ROS production by targeting the mitochondrial respiratory chain complex, promoting resistance and driving tumor progression [31]. Research by Cui et al. [32] demonstrated that a salicylic acid-based compound, SH-4-54, induces apoptosis in temozolomide-resistant glioblastoma cells by triggering mitochondrial signal transducer and activator of transcription-3 (STAT3) translocation and respiratory chain dysfunction.

In conclusion, mitochondrial respiratory chain dysfunction plays diverse and complex roles in tumor cells, affecting not only cellular energy metabolism but also influencing growth, invasion, and drug resistance through the regulation of ROS levels and apoptotic signaling pathways. Therefore, in-depth research and understanding of the mechanisms by which mitochondrial respiratory chain

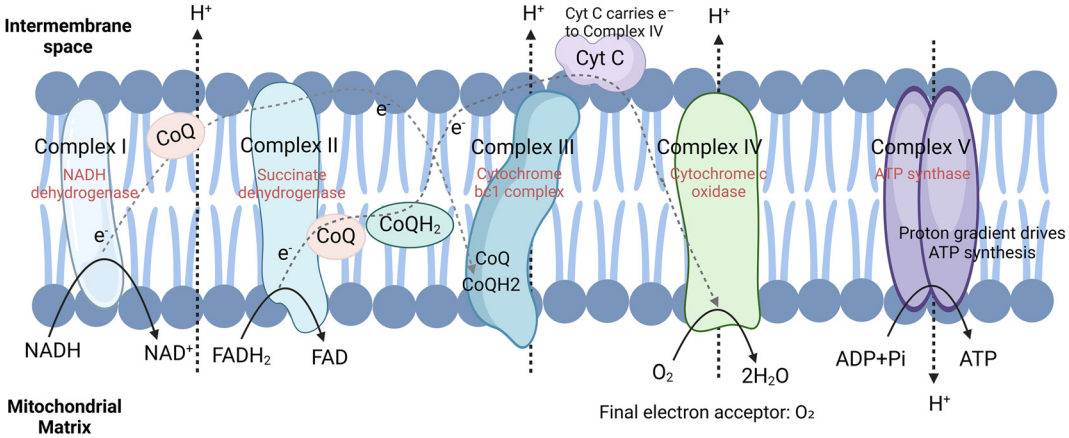

Figure 2: The mitochondrial respiratory chain and oxidative phosphorylation (OXPHOS). This figure illustrates the mitochondrial electron transport chain (ETC) embedded in the inner mitochondrial membrane. Electrons from NADH and $FADH_2$ are transferred to oxygen (O_2), the final electron acceptor, through protein complexes (complexes I–IV) via coenzyme Q (CoQ) and cytochrome *c* (Cyt C). This process generates water (H_2O) and releases energy, which is used to pump protons (H^+) from the mitochondrial matrix into the intermembrane space, creating a proton gradient. Complex V (ATP synthase) utilizes this gradient to drive ATP synthesis, converting ADP and inorganic phosphate (Pi) into ATP, providing energy for cellular processes.

dysfunction impacts tumor biology are crucial for developing novel anti-cancer drugs and improving the efficacy of cancer therapies.

Mitochondrial metabolic reprogramming and tumor development

Warburg effect and glycolytic pathway

The Warburg effect, a hallmark of tumor metabolic reprogramming, describes tumor cells preferring glycolysis over OXPHOS for energy metabolism, even with adequate oxygen. This unique adaptation strategy not only reflects the specific energy demands of tumor cells but also promotes tumor progression in multiple ways [33]. From the perspective of energy supply, glycolysis – with its rapid and efficient characteristics – becomes the preferred pathway for the fast proliferation of tumor cells. Although each glucose molecule produces far less ATP via glycolysis compared to OXPHOS, the rate of glycolysis ensures that tumor cells can obtain sufficient energy in a short period, which is essential for sustaining rapid growth and division [34]. Additionally, glycolysis intermediates are crucial for tumor development, supporting biosynthesis and metabolic adaptation. The Warburg effect enhances glucose uptake and channels glycolytic intermediates into pathways for synthesizing nucleic acids, lipids, and proteins, thereby providing the material foundation necessary for tumor cell growth, proliferation, and metastasis [35]. For example, lactate, the main by-product of glycolysis, acidifies the TME, which then activates signaling pathways related to tumor invasion and metastasis. Martinez-Outschoorn et al. [36] demonstrated, from a metabolic genomics perspective, how lactate enhances cancer cell "stemness," promoting breast cancer recurrence, metastasis, and adverse clinical outcomes. Furthermore, pyruvate, another critical intermediate, can be converted into acetyl-CoA to enter the tricarboxylic acid (TCA) cycle or used for the synthesis of biomacromolecules like fatty acids and cholesterol, essential for tumor cell growth and membrane stability. Feng et al. [37] confirmed that phosphoglycerate mutase 1 (PGAM1) promotes the production of pyruvate and/or lactate in ovarian cancer cells, enhancing paclitaxel resistance, thereby offering new therapeutic insights for reversing ovarian cancer drug resistance. Beyond meeting energy needs and providing intermediate metabolites, glycolysis activation is closely linked to immune evasion and drug resistance in tumor cells [38, 39]. Glycolytic metabolites like lactate can inhibit immune cell activity, helping tumor cells evade immune surveillance and attack. Key enzymes in the glycolytic pathway, such as hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK), are often overexpressed or mutated in tumor cells. This not only reinforces glycolysis as the dominant energy pathway but also contributes to increased resistance to chemotherapy drugs in tumor cells [40].

In conclusion, the Warburg effect, through its distinctive mechanism of metabolic reprogramming, satisfies the energy demands of rapidly proliferating tumor cells while playing significant roles in TME acidification, macromolecule synthesis, immune evasion, and drug resistance. A deep understanding of the Warburg effect and its molecular mechanisms is crucial for developing novel anti-tumor therapies and strategies to overcome tumor resistance.

Glutamine metabolism

Glutamine metabolism is a crucial strategy for tumor cells to adapt to rapid proliferation and metabolic stress. As a non-essential amino acid, glutamine is converted into glutamate by the enzyme glutaminase (GLS), providing nitrogen for tumor cells and generating α-ketoglutarate (α-KG), which enters the TCA cycle to participate in energy production and biosynthesis. Overexpression of GLS in tumor cells ensures efficient utilization of glutamine, thereby meeting the demands of rapid tumor growth [41]. In addition to entering the TCA cycle, glutamine is also converted into citrate via the reductive carboxylation pathway, which is used for the biosynthesis of lipids and nucleotides. The fatty acids, cholesterol, and other lipid components, as well as purine and pyrimidine nucleotides, produced through this pathway, are essential for maintaining the membrane structure, signal transduction, and DNA replication in tumor cells [42, 43].

Activation of glutamine metabolism has been observed in various tumor types, providing essential biosynthetic precursors and energy for tumor cells. Research indicates that inhibiting glutamine metabolism can suppress tumor progression. For example, progesterone inhibits the growth of endometrial cancer by suppressing glutamine metabolism via targeting the alanine/serine/cysteine transporter 2 (ASCT2) [44]; circDYRK1A mediated by RUNX family transcription factor 3 (RUNX3) upregulates microRNA-889-3p-dependent F-box protein 4 (FBXO4) to inhibit glutamine metabolism in gastric cancer [45]; radiation-induced exosomes promote oral squamous cell carcinoma progression by enhancing solute carrier family 1 member 5 (SLC1A5)-mediated glutamine metabolism [46]; disruption of Yes1 associated transcriptional regulator (YAP1)-mediated

glutamine metabolism induces synthetic lethality in osteosarcoma while suppressing ornithine decarboxylase 1 (ODC1) [47]. These studies underscore the central role of glutamine metabolism in tumor development. Research by Yokoyama et al. [48] using metabolomics analysis demonstrated that Sirpiglenastat (DRP-104) induces anti-tumor effects by directly antagonizing glutamine metabolism and stimulating the immune system, revealing the therapeutic potential of targeting glutamine metabolism. It is important to note that glutamine metabolism does not function in isolation but is tightly interconnected with other metabolic pathways. For example, its synergistic effect with glycolysis provides sufficient energy and biosynthetic precursors for tumor cells [49, 50]. Furthermore, various signaling pathways, such as the PI3K/Akt/mTOR pathway, also regulate glutamine metabolism, and abnormal activation of these pathways further promotes tumor progression [51, 52].

In conclusion, glutamine metabolism in tumor cells is a highly complex and crucial process. It not only provides essential biosynthetic precursors and energy for tumor cells but also intertwines with other metabolic pathways and signaling networks to drive tumor development.

Fatty acid oxidation

Fatty acid oxidation is one of the key pathways in mitochondrial metabolism, where fatty acids are gradually broken down into acetyl-CoA through β-oxidation. The acetyl-CoA then enters the TCA cycle to generate ATP, providing energy for the cell (Figure 3) [53, 54]. In the metabolic network of tumor cells, activation of fatty acid oxidation has become an important feature of tumor metabolic reprogramming, profoundly influencing tumor growth, invasion, and metastasis [55].

First, fatty acid oxidation provides a stable and abundant energy source for tumor cells. Due to rapid proliferation, tumor cells have a high energy demand. Under conditions of glucose deprivation or hypoxia, fatty acid oxidation serves as an efficient energy-producing pathway, allowing tumor cells to maintain survival and proliferation [56]. Second, the metabolic byproducts of fatty acid oxidation, such as NADH and $FADH_2$, not only contribute to ATP generation but also serve as electron carriers in the electron transport chain, promoting the production of ROS. Moderate levels of ROS act as signaling molecules, activating pathways associated with tumor cell proliferation and invasion, further driving malignant progression [57–59]. The role of fatty acid oxidation in the TME has also attracted research attention. For instance, Lu et al. [60] revealed that under hypoxic conditions, tumor-derived exosomes regulate fatty acid oxidation via miR-4488 and RTN3/FABP5 (reticulon 3/fatty acid binding protein 5), inducing M2 macrophage polarization and ultimately promoting liver metastasis in pancreatic neuroendocrine tumors. This highlights the complex role of fatty acid oxidation in TME regulation and

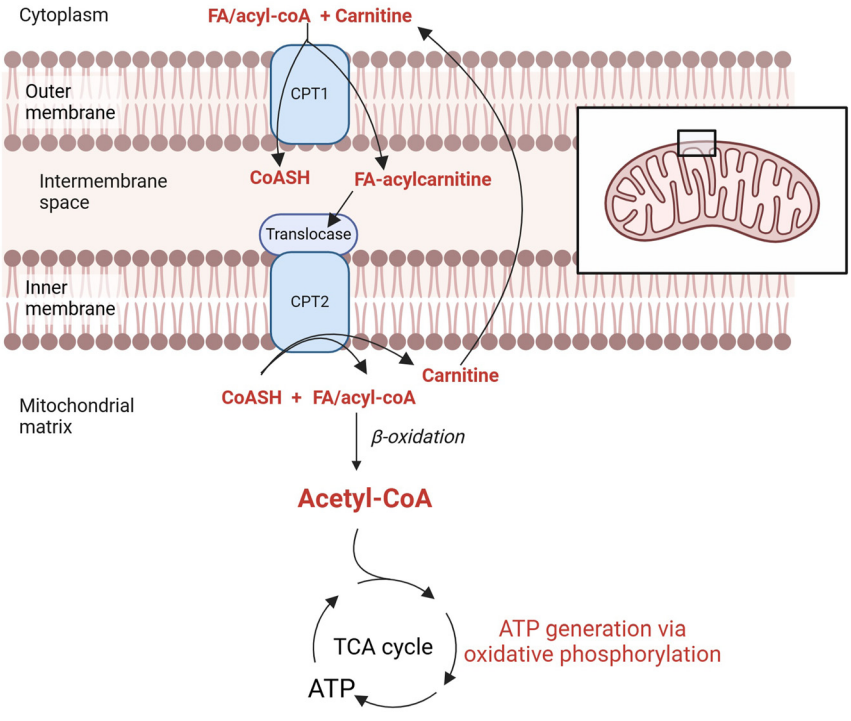

Figure 3: Fatty acid oxidation and the carnitine shuttle system in mitochondrial metabolism. Fatty acid oxidation is a key mitochondrial metabolic pathway where fatty acids are transported into the mitochondria via the carnitine shuttle system. CPT1 (Carnitine Palmitoyl transferase 1) catalyzes the conversion of fatty acyl-CoA to fatty acylcarnitine, allowing transport across the outer mitochondrial membrane. After being transported into the mitochondrial matrix via translocase, CPT2 (Carnitine Palmitoyl transferase 2) converts fatty acylcarnitine back to fatty acyl-CoA, releasing free carnitine. The fatty acyl-CoA undergoes β-oxidation, producing acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle. ATP is subsequently generated via oxidative phosphorylation, providing energy for cellular processes.

tumor progression. Fatty acid oxidation is not only associated with energy supply in tumor cells but is also closely linked to immune evasion and drug resistance. By enhancing antioxidant capacity, fatty acid oxidation helps tumor cells resist oxidative stress and immune system attacks, thereby providing a survival advantage [61]. At the same time, some anti-tumor drugs function by inducing oxidative stress and apoptosis in tumor cells, but activation of the fatty acid oxidation pathway may diminish the effectiveness of these drugs, leading to drug resistance and increasing the difficulty of tumor treatment [62, 63].

In conclusion, fatty acid oxidation plays a crucial role in multiple aspects of tumor biology, including energy supply, invasion, metastasis, immune evasion, and drug resistance. A deeper understanding of the molecular mechanisms underlying this metabolic reprogramming and its association with tumor progression will provide important theoretical foundations and potential targets for the development of novel anti-tumor drugs targeting fatty acid oxidation pathways.

The pentose phosphate pathway (PPP) and nucleotide biosynthesis

The pentose phosphate pathway (PPP) is an indispensable part of the metabolic reprogramming in tumor cells. This pathway generates NADPH and pentose phosphates through the oxidative metabolism of glucose, providing essential precursors for antioxidant defense, nucleotide biosynthesis, and lipid synthesis. In this way, it supports tumor cell survival and proliferation on multiple levels [64, 65].

The PPP can be divided into the oxidative and non-oxidative phases. In the oxidative phase, glucose-6-phosphate is oxidized to form 6-phosphoglucono-δ-lactone, which is subsequently converted into 5-phosphoribulose. In this process, each molecule of glucose-6-phosphate is oxidized, generating two molecules of NADPH and one molecule of CO_2. NADPH, a potent reductant, neutralizes ROS generated within the cell, effectively protecting the cell from oxidative stress damage [66]. Given that tumor cells are metabolically active and generally exhibit high ROS levels, the NADPH produced by the PPP is particularly important in maintaining the redox balance of tumor cells, serving as a critical line of defense against oxidative damage [67].

In addition to its antioxidant function, the PPP also provides key precursors for nucleotide biosynthesis through its non-oxidative phase. In this phase, 5-phosphoribulose is catalyzed by transketolase and transaldolase to form glyceraldehyde-3-phosphate and fructose-6-phosphate, which can re-enter the glycolytic pathway or be converted into other biomolecules. Intermediate products of the PPP, such as ribose-5-phosphate, are key precursors for nucleotide biosynthesis, supporting DNA replication and genetic information transmission in tumor cells [68, 69].

Activation of the PPP has been observed in various types of tumors, significantly enhancing tumor cell growth and invasiveness. For instance, the activation of the PPP pathway in certain leukemia and lymphoma cells is positively correlated with the malignancy of the tumor cells [70]. Additionally, some anticancer drugs exert their effects by inhibiting the PPP, blocking the energy supply and biosynthesis processes in tumor cells, providing a novel approach for targeting the PPP in cancer therapy [71].

In conclusion, the PPP, through its roles in antioxidant defense and nucleotide biosynthesis, profoundly influences the biological behavior of tumor cells. Future research should further explore the specific mechanisms of the PPP in different tumor types and investigate how precise modulation of the PPP can improve cancer treatment outcomes and enhance patient quality of life.

Emerging role of Mitochondrial Dynamics (MD) in cancer

Mitochondria are not only central to cellular energy metabolism, but also regulate cell growth, differentiation, apoptosis, and stress adaptation through their dynamics. Mitochondrial dynamics (MD) refers to the processes of mitochondrial fission and fusion, which maintain a dynamic balance within the cell to ensure energy supply and metabolic homeostasis. Mitochondrial fission helps clear damaged mitochondria, while the fusion process restores mitochondrial function and maintains metabolic stability. Under normal physiological conditions, the balance between mitochondrial fission and fusion is crucial for maintaining cellular function. However, in various cancers, the imbalance of MD has become a hallmark of cancer cells, significantly affecting cancer progression and treatment response. For example, studies have shown that Caveolin-1, by regulating the activity of MD-related proteins (such as mitofusin 2 (MFN2) and dynamin-related protein 1 (DRP1)) and mitochondrial autophagy, alters the mitochondrial morphology, damage accumulation, and ROS production in cancer cells, thus revealing the critical role of MD in cancer cell survival and treatment resistance [72].

The increase in mitochondrial fission is closely related to tumor proliferation, invasiveness, and metastatic ability [73]. For instance, overexpression of DRP1 or downregulation of MFN1 enhances mitochondrial fission or inhibits

mitochondrial fusion, leading to the redistribution of mitochondria to the pseudopod region, thereby promoting migration and invasion of breast cancer cells [74]. Under hypoxic conditions, DRP1 enhances the migration ability of glioblastoma U251 cells by promoting mitochondrial fission [75]. In contrast, changes in mitochondrial fusion exhibit dual effects: on one hand, increased mitochondrial fusion can inhibit tumor growth by enhancing mitochondrial autophagy. For example, a study by Yu et al. [76] showed that inhibition of mitochondrial fission in pancreatic cancer cells increased fusion, thereby suppressing tumor growth by enhancing mitochondrial autophagy, reducing mitochondrial mass, and decreasing ATP production. On the other hand, increased mitochondrial fusion can also promote tumor cell migration and metabolism. For instance, mitochondrial fusion mediated by optic atrophy 1 (OPA1) and MFN1 in liver cancer cells promotes tumor growth and cell proliferation by regulating metabolism [77]. In triple-negative breast cancer, enhanced mitochondrial fission inhibited cell migration, invasion, and metastasis through the suppression of signaling pathways such as PI3K/Akt/mTOR and Ras/Raf/MEK/ERK, thus suppressing cancer progression; whereas activation of mitochondrial fusion could overcome the inhibitory effects of fission on these processes [78]. Additionally, the potential of mitochondrial fusion as a therapeutic target has gained attention in cancer treatment. For example, studies have shown that targeting mitochondrial fusion, particularly inhibiting MFN2 or OPA1, can significantly inhibit the growth of acute myeloid leukemia cells with minimal effects on normal cells [79].

In summary, MD, by regulating the balance between fission and fusion, influences the migration, invasion, and metabolism of cancer cells. In various types of cancer, mitochondrial fission and fusion play significant roles in tumor growth, metastasis, and response to treatment. Therefore, the regulation of MD has emerged as a potential cancer therapeutic strategy, providing new directions for further research.

Targeting mitochondria in tumor therapy

Inhibition of mitochondrial function

Inhibiting mitochondrial function is an important strategy in targeted cancer therapy, aiming to weaken or suppress the growth and proliferation of tumor cells by disrupting the normal physiological functions of mitochondria. Mitochondria, as the “energy factories” of cells, play a central role in cellular metabolism. By intervening in mitochondrial function through precise methods, it is possible to effectively block the energy supply chain of tumor cells, thereby achieving anti-cancer therapeutic goals [80]. Among the various methods for inhibiting mitochondrial function, targeting mitochondrial respiratory chain complexes has emerged as a promising and effective approach. Inhibiting the activity of these complexes significantly reduces ATP production efficiency, pushing tumor cells into an energy crisis that impairs their growth (Table 1) [81]. For instance, cisplatin and paclitaxel have been shown to damage mtDNA or bind to respiratory chain complexes, inhibiting their activity and inducing apoptosis and necrosis in tumor cells [82, 83]. Furthermore, interfering with the replication and transcription of mtDNA is another effective way to inhibit mitochondrial function. This method would suppress the energy metabolism of tumor cells by inducing mitochondrial dysfunction, which would activate intrinsic apoptotic pathways in tumor cells and accelerate their death.

Mitochondrial-targeting therapies can also synergize with other anti-tumor treatments to enhance their efficacy [84]. For example, certain mitochondrial-targeting drugs significantly increase the sensitivity of tumor cells to radiotherapy and chemotherapy, improving the therapeutic effect when these conventional therapies are combined. Chen et al. [85] innovatively used tumor-targeting near-infrared (NIR) anthocyanine dye (IR-808) as both a targeting ligand and a NIR fluorescence probe to successfully deliver hypoxia-affinity nitroimidazole compounds to the mitochondria of cancer cells, achieving synergistic effects in radiochemotherapy. Additionally, inhibiting mitochondrial function can induce immunogenic cell death (ICD) in tumor cells, thereby activating anti-tumor immune responses and enhancing the anti-tumor effect. For instance, *in situ* administration of mitochondrial-targeted ICD inducers can effectively trigger CD8+ T cell-dependent anti-tumor immune responses, providing new avenues for cancer immunotherapy [86]. Moreover, the use of mitochondrial-targeted magnetic hyperthermia-based immunogenic cell death strategies can induce functional reprogramming of tumor-associated macrophages, further enhancing the effectiveness of cancer immunotherapy [87].

In conclusion, inhibiting mitochondrial function as a targeted cancer therapy strategy weakens tumor cell growth and proliferation, enhances synergy with other therapeutic approaches, and induces immunogenic cell death to activate anti-tumor immune responses. These findings deepen our understanding of the role of mitochondria in tumorigenesis and progression and provide an important theoretical basis and practical guidance for the development of novel anti-tumor drugs and therapeutic strategies.

Table 1: Comparison of mitochondrial-targeted therapies in cancer treatment.

Therapy	Mechanism	Advantage	Weakness	Difference
Mitochondrial function inhibition	By inhibiting the activity of mitochondrial respiratory chain complexes and reducing ATP production, mitochondrial function inhibition leads to an energy crisis in tumor cells.	1) Strongly inhibits tumor cell proliferation 2) Enhances sensitivity to conventional therapies 3) Activates immune cell death (ICD)	1) May impact the energy metabolism of normal cells 2) Toxicity concerns, requiring cautious application	Primarily relies on the mitochondrial respiratory chain, suitable for various tumors, and can enhance the effects of chemotherapy and radiotherapy.
Interference with mitochondrial metabolic pathways	By inhibiting glutamate metabolism, fatty acid oxidation, and other pathways, this strategy blocks the synthesis precursors and energy sources of tumor cells.	1) High specificity and selectivity 2) Reduces reliance on traditional chemotherapy drugs 3) Lowers treatment burden	1) Currently limited to preclinical research 2) Limited effectiveness for certain types of tumors	Focusing on metabolic pathway intervention, this approach precisely targets tumor cells while avoiding the side effects of conventional treatments.
Utilizing mitochondria-mediated apoptosis	By increasing mitochondrial outer membrane permeability, pro-apoptotic factors such as cytochrome *c* are released, activating the caspase cascade.	1) Precisely induces tumor cell apoptosis. 2) Increases treatment specificity. 3) Can be combined with other therapies.	1) Anti-apoptotic mechanisms exist, allowing tumor cells to evade apoptosis. 2) Ineffective against certain tumor cells.	Focused on activating apoptosis, this approach is particularly suitable for tumor types that rely on apoptosis.

Interference with mitochondrial metabolic pathways

Interfering with mitochondrial metabolic pathways is a highly precise and promising strategy for targeted cancer therapy. By inhibiting key metabolic steps such as glutamine metabolism, fatty acid oxidation, or the PPP, it is possible to cut off the supply of biosynthetic precursors and energy sources for tumor cells, thereby suppressing their growth and invasive potential (Table 1) [88]. The core advantage of this strategy lies in its high specificity and selectivity. By exploiting the inherent metabolic differences between tumor cells and normal cells, inhibitors targeting tumor-specific metabolic pathways can be designed to precisely target tumor cells. This approach not only reduces reliance on traditional chemotherapy drugs, thereby alleviating the treatment burden and side effects for patients but also holds the potential to significantly enhance therapeutic efficacy and improve patient quality of life. This concept of precision therapy based on metabolic differences represents an important direction for future cancer treatment. Several novel targeted therapies in this field have already shown promising application prospects. For example, glutaminase inhibitors and fatty acid synthase inhibitors are showing potential in preclinical and clinical trials. Among these, the combination of 5-fluorouracil and the glutaminase inhibitor CB-839 has been shown to enhance anti-tumor activity in PIK3CA-mutant colorectal cancer [89]. Additionally, the small molecule fatty acid synthase inhibitor MFI03 has demonstrated excellent activity against PC3 tumor cells by inducing cell cycle arrest and inhibiting cell division [90].

In conclusion, targeted therapies that interfere with mitochondrial metabolic pathways, with their high specificity and selectivity, provide new approaches and strategies for cancer treatment. As research continues to deepen and novel drugs emerge, we have strong reasons to believe that this strategy will play an increasingly important role in future cancer therapies.

Exploitation of mitochondrial-mediated apoptosis

By precisely triggering mitochondria-mediated apoptotic pathways, tumor cells can be effectively induced to undergo programmed cell death, thereby achieving therapeutic goals in cancer treatment (Table 1) [91]. This process primarily relies on two core steps: the first is the significant increase in mitochondrial outer membrane permeability (MOMP), which leads to the release of pro-apoptotic factors such as Cyt *c* from the mitochondria into the cytoplasm; subsequently, these released pro-apoptotic factors further activate the caspase cascade, leading to apoptosis. In this complex and intricate process, the Bax/Bak protein family plays a

critical regulatory role. In their resting state, these proteins exist in an inactive form in the cytoplasm, and upon receiving apoptotic signals, they undergo conformational changes and oligomerize on the mitochondrial outer membrane, increasing its permeability and facilitating the release of pro-apoptotic factors [92]. After Cyt *c* is released, it binds closely to apoptotic protease activating factor-1 (APAF-1) to form the apoptosome, activating caspase-9 and triggering the caspase cascade. This cascade then activates effector caspases, such as caspase-3 and caspase-7, which ultimately induce hallmark events of apoptosis, including nuclear DNA fragmentation, cytoskeletal disruption, and membrane blebbing [93, 94].

In recent years, innovative therapies utilizing mitochondria-mediated apoptotic pathways have made significant progress, such as photodynamic therapy (PDT) and sonodynamic therapy (SDT). Both therapies induce mitochondrial damage by generating ROS, which, in turn, trigger apoptotic pathways. PDT uses photosensitizers that undergo photochemical reactions when exposed to light of specific wavelengths, producing large amounts of ROS, leading to a decrease in mitochondrial membrane potential and an increase in MOMP, thus promoting the release of pro-apoptotic factors. Similarly, SDT utilizes ultrasound to activate sonosensitizers, generating ROS that induce mitochondrial damage and apoptosis [95, 96]. It is important to note that mitochondria-mediated apoptosis pathways interact complexly with other forms of cell death. For example, mitochondrial damage and excessive ROS production can not only trigger apoptosis but also activate ferroptosis, necroptosis, and other forms of cell death, thus broadening the diversity of cell death mechanisms [97, 98]. However, to evade mitochondria-mediated apoptosis, tumor cells often employ various strategies, such as upregulating anti-apoptotic proteins or altering mitochondrial metabolic pathways. The existence of these mechanisms undoubtedly increases the complexity and challenges in cancer treatment.

Therefore, when developing anti-cancer therapies that exploit mitochondria-mediated apoptotic pathways, it is essential to fully consider these complexities and diversities. In-depth studies of the apoptotic resistance mechanisms in tumor cells are necessary to continuously optimize and innovate treatment strategies, with the goal of achieving more precise, efficient, and safe cancer therapies. Future research should focus on uncovering the intrinsic connections between mitochondria-mediated apoptosis and other forms of cell death, as well as exploring how to effectively overcome tumor cell resistance to apoptosis, opening new avenues for cancer treatment.

Mitochondrial-targeting drug delivery systems

The efficient delivery of mitochondrial-targeted drugs to tumor cells has become a significant challenge, largely due to the mitochondria's deep location within the cell and their double-layer membrane structure. In response to this challenge, researchers have focused on developing diverse mitochondrial-targeted drug delivery systems in recent years, with nanoparticles, liposomes, and peptides being of particular interest. Nanoparticles offer unique advantages in mitochondrial-targeted drug delivery.

Through surface modification and functional design, nanoparticles can carry mitochondrial-targeted drugs across the cell membrane and deliver them precisely to the mitochondria via electrostatic interactions, hydrophobic effects, or receptor-mediated endocytosis [99]. This delivery approach not only improves the bioavailability of the drug but also enhances its mitochondrial targeting, providing a novel strategy for cancer treatment.

Liposomes are also widely used in mitochondrial-targeted delivery due to their excellent biodegradability and biocompatibility. Liposomes encapsulate drugs within small spherical structures formed by phospholipid bilayers, offering effective protection to the drugs while significantly enhancing their affinity and targeting to the mitochondria through surface modification with specific targeting molecules, such as triphenylphosphine (TPP) [100, 101]. Once inside the cell, the drug is rapidly released from the liposome and reaches the mitochondria to exert its anti-tumor effects.

Additionally, peptides have gradually become an important tool for mitochondrial drug delivery due to their inherent biological stability and targeting functions. By designing and synthesizing peptide sequences with mitochondrial-targeting capabilities, researchers have achieved precise drug delivery. This method not only exhibits high specificity and targeting ability but also maintains stability in complex biological environments, offering new possibilities for cancer treatment [102].

In addition to the aforementioned delivery systems, novel mitochondrial-targeted drug delivery systems, such as polymer micelles and inorganic nanomaterials, are also under investigation. These systems each have unique characteristics and can be flexibly selected and designed according to the properties of the drug and delivery requirements, providing a broader range of options for mitochondrial-targeted drug delivery [103].

In conclusion, significant progress has been made in the research of mitochondrial-targeted drug delivery systems, offering new hope for cancer therapy. However, optimizing

these delivery systems to further improve drug delivery efficiency and targeting remains a critical focus of future research. With continuous advancements in science and technology, mitochondrial-targeted drug delivery systems will play an increasingly important role in cancer treatment.

Mitochondria and tumor immunity

Mitochondrial damage and the release of damage-associated molecular patterns (DAMPs)

Following mitochondrial damage, a series of damage-associated molecular patterns (DAMPs) are released, including mtDNA, ATP, calreticulin (CRT), and high-mobility group box 1 (HMGB1), each of which has unique molecular structures and biological functions that can activate various types of immune cells, thereby triggering effective anti-tumor immune responses [104, 105]. Firstly, mtDNA, lacking histone protection, is more prone to damage and release into the extracellular space compared to nuclear DNA. The released mtDNA activates the Toll-like receptor 9 (TLR9) signaling pathway, inducing dendritic cell (DC) maturation and T cell activation, thereby significantly enhancing antigen presentation and T cell-mediated anti-tumor immunity [106, 107]. This mechanism not only reveals the direct role of mitochondria in immune activation but also highlights the potential of mtDNA as an immunogenic molecule. Secondly, ATP is released into the extracellular space upon mitochondrial damage, where it activates the P2X7 receptor to trigger a series of immune responses [108]. Extracellular ATP induces macrophages and DCs to secrete inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin-1 (IL-1), as well as chemokines, which further recruit and activate natural killer (NK) cells and T cells, forming a robust anti-tumor immune network [109, 110]. This discovery deepens our understanding of ATP's role in immune modulation and provides a theoretical basis for the development of ATP-based immunotherapy strategies. In addition, CRT and HMGB1 are other important DAMPs released following mitochondrial damage. CRT is released to the cell surface after mitochondrial damage, serving as an "eat me" signal to promote the phagocytosis of tumor cells by macrophages and DCs and enhance antigen presentation, thereby improving the immune system's ability to recognize and eliminate tumor cells [111]. HMGB1, released into the extracellular space following cellular damage or death, binds to receptors such as RAGE and TLR4, activating DCs and macrophages, and promoting the secretion of inflammatory cytokines and T cell activation, further amplifying the anti-tumor immune response [112].

In conclusion, DAMPs released after mitochondrial damage activate different types of immune cells, triggering complex immune network responses that effectively inhibit tumor growth and spread. Future research should further explore the potential of these DAMPs in cancer immunotherapy to develop more efficient and safe immunotherapeutic strategies. Additionally, attention should be paid to the relationship between mitochondrial damage and tumor immune evasion in order to fully understand the complex roles of mitochondria in tumorigenesis and progression.

Mitochondrial dysfunction and immune cell metabolism

Mitochondrial dysfunction affects not only the tumor cells themselves but also indirectly regulates the metabolic state and activity of immune cells, thereby influencing the TME [113]. The TME, characterized by hypoxia, nutrient deficiency, and acidity, imposes severe survival pressures on immune cells, especially T cells. As the core players in anti-tumor immunity, the mitochondrial functional state of T cells directly determines their activity and function. Under hypoxic conditions, T cells face a blockade of the mitochondrial OXPHOS pathway, leading to reduced ATP production. To overcome this challenge, T cells undergo metabolic reprogramming, relying on glycolysis to rapidly generate energy. However, this short-term adaptation strategy has long-term negative consequences, including a reduction in T cell proliferation, weakened cytotoxicity, and impaired memory cell formation, which significantly diminishes the T cell-mediated anti-tumor immune response, thus creating opportunities for tumor cells to evade immune surveillance [114–116]. In addition to hypoxia, tumor cells also secrete metabolic byproducts that further disrupt the mitochondrial function of immune cells. For example, the large amounts of lactate produced by tumor cell glycolysis acidify the TME, directly impairing T cell mitochondrial function [117, 118]. Meanwhile, arginase secreted by tumor cells degrades arginine, a crucial molecule for T cell mitochondrial function, further weakening T cell activity [119, 120]. Not only are T cells affected, but the TME also significantly impacts the mitochondrial function of macrophages and natural killer (NK) cells. In the TME, macrophages are polarized into the M2 phenotype, which is associated with reduced OXPHOS levels and enhanced glycolytic activity, promoting tumor growth and angiogenesis [121]. NK cells are also influenced by the TME,

with mitochondrial dysfunction leading to weakened cytotoxicity and reduced anti-tumor activity [122].

NAD+ is a key coenzyme in immune cell metabolism, regulating mitochondrial function and metabolic pathways. During the activation of T cells and macrophages in immune responses, NAD+ maintains the energy balance of immune cells by regulating mitochondrial metabolic pathways such as OXPHOS and glycolysis [123]. However, mitochondrial dysfunction in the TME often leads to increased NAD+ consumption, which limits the energy supply to immune cells and weakens their anti-tumor capabilities [124]. Tumor cells reduce NAD+ levels in immune cells by secreting NAD+ degrading enzymes, such as CD38, thereby inhibiting immune cell function [125]. Targeting NAD+ degrading enzymes or enhancing NAD+ synthesis can restore the metabolic state of immune cells and boost their anti-tumor ability [126–128]. NAD+ targeted therapies, particularly through the inhibition of NAD+ degrading enzymes, have emerged as novel immunotherapeutic strategies. This approach not only restores immune cell function but also improves their survival in the hypoxic, acidic, and nutrient-deprived TME, thereby enhancing the immune response. Moreover, NAD+ targeting strategies may synergize with monoclonal antibody treatments, enhancing immune responses by restoring immune cell function. For instance, CD38 inhibitors can reduce NAD+ consumption, restore immune cell energy metabolism and anti-tumor function, and when combined with monoclonal antibody therapies (e.g., anti-PD-1), they enhance T cell anti-tumor responses [129].

In conclusion, mitochondrial dysfunction alters the metabolic state and activity of both tumor and immune cells, shifting the dynamic balance of the tumor immune microenvironment. This shift weakens the immune system's anti-tumor response, providing favorable conditions for tumor growth and spread. Therefore, therapeutic strategies targeting mitochondrial dysfunction, such as restoring mitochondrial function in immune cells or enhancing anti-tumor immune responses through NAD+ targeting, may become new directions for future cancer treatment.

Mitochondria-targeted immunotherapy

Mitochondrial-targeted immunotherapy is gradually emerging as a frontier in cancer treatment research. Unlike those methods, which aim to inhibit tumor growth by targeting mitochondria within the tumor cells themselves, mitochondria-targeted immunotherapy enhances the immune system's ability to combat cancer by leveraging mitochondrial-mediated mechanisms to modulate immune cell function and activity. This approach not only activates mitochondrial-driven apoptosis pathways in tumor cells but also improves the metabolic status of immune cells, promoting a more effective anti-tumor immune response. Mitochondria-targeted immunotherapy specifically works through several mechanisms. First, it enhances immune cell function by optimizing mitochondrial performance, which is crucial for maintaining energy production and cellular metabolism in immune cells, thus boosting their anti-tumor activity. For example, mitochondrial-targeted nutritional supplements or drugs can be administered to immune cells to improve their mitochondrial function, resulting in improved efficacy in fighting cancer [130]. Second, this immunotherapy approach facilitates the release of DAMPs from tumor cells, which in turn activate immune responses [131]. It also involves the modulation of immune checkpoint inhibitors, such as programmed cell death 1 (PD-1) and Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibodies, which block immunosuppressive signals in the TME and activate key effector cells like T cells. By overcoming tumor immune evasion, these treatments enhance the immune system's ability to attack tumors more efficiently [132]. Moreover, the combination of mitochondria-targeted immunotherapy with chimeric antigen receptor T (CAR-T) cell therapy and tumor vaccines further improves the efficacy and safety of immunotherapy. CAR-T cell therapy genetically engineers T cells to express chimeric antigen receptors (CARs), allowing them to target and kill tumor cells specifically [133]. Similarly, tumor vaccines enhance the immune system by introducing tumor-specific antigens or cells, thereby further stimulating the anti-tumor immune response [134].

In summary, mitochondrial-targeted immunotherapy enhances the anti-tumor capacity of the immune system through multidimensional and multifaceted regulatory mechanisms. As research continues to advance and technology progresses, these therapies are expected to play an increasingly important role in cancer treatment, offering improved therapeutic prospects for patients. At the same time, further exploration of the potential links between mitochondria and other immune regulation pathways may lead to the development of more efficient and safer cancer immunotherapy strategies.

Clinical applications and challenges

While mitochondrial-targeted therapies have advanced in basic research, their clinical translation faces significant challenges. Currently, drugs targeting mitochondrial respiratory chain complexes or interfering with mitochondrial

metabolic pathways have shown preliminary anti-tumor potential in preclinical and clinical trial evaluations. For example, IACS-010759, an inhibitor targeting mitochondrial complex I, has also shown promising results in preclinical studies and is now being evaluated in clinical trials for advanced solid tumors and acute myelogenous leukemia [135, 136]. However, the efficacy and safety of these drugs still require more rigorous and comprehensive validation and optimization. A core challenge is delivering mitochondrial-targeted drugs to tumor cells precisely while minimizing toxicity to normal cells. Furthermore, finding ways to integrate these emerging therapies with existing cancer treatment modalities to synergistically enhance therapeutic outcomes remains an urgent issue. The diversity and complexity of mitochondrial functions, as well as significant differences between tumor types and individual patients, could have profound impacts on the actual efficacy and safety of these targeted therapies [137].

Given these challenges, future research should focus on several key directions: Firstly, further optimization of mitochondrial-targeted drug delivery systems to ensure precise targeting and efficient release of drugs; secondly, deepening the exploration of new mitochondrial-related targets and developing innovative therapeutic strategies targeting these pathways; and finally, enhancing our understanding of the specific mechanisms by which mitochondria contribute to tumor initiation and progression, in order to provide a more comprehensive understanding of their role in tumor biology and support personalized treatment approaches. By addressing these challenges, we can overcome the current obstacles and promote the widespread clinical application of mitochondrial-targeted therapies, offering more effective treatment options for cancer patients.

Conclusion and prospects

Mitochondria, as the central organelles within cells, play indispensable roles in tumorigenesis, tumor progression, and therapeutic response. The function and metabolic state of mitochondria undergo dynamic changes throughout the tumor process, profoundly influencing the biological characteristics of tumor cells and their treatment sensitivity. In addition to providing energy and material resources, mitochondria regulate processes such as apoptosis, proliferation, and metabolic reprogramming, which significantly impact tumor cell biology.

As cancer therapies continue to evolve, mitochondria remain a critical target for therapeutic innovation [138]. Recent cutting-edge studies have revealed exciting new directions in mitochondrial medicine, particularly in the development of therapies that exploit mitochondrial dysfunction as a mechanism for selectively killing cancer cells. For example, mitochondria-targeted prodrugs that accumulate in tumor cells have shown promising potential in preclinical models, enabling the delivery of therapeutics directly to the mitochondria, enhancing efficacy and minimizing off-target effects [139, 140]. Additionally, mitochondrial fusion and fission modulators, which regulate mitochondrial dynamics, are being explored as potential therapeutic agents to counteract the metabolic plasticity of cancer cells [141, 142]. One particularly innovative approach involves the use of mitochondrial ROS-targeting strategies, where increasing ROS levels within tumor cells can overwhelm their antioxidant defenses, selectively targeting cancerous cells while sparing normal tissues [143]. Moreover, mitochondrial-targeted immunotherapies, which aim to enhance the mitochondrial function of immune cells, are being developed to boost the anti-tumor immune response. For instance, targeting mitochondrial apoptosis pathways has been proposed as a way to sensitize tumors to immunotherapy, particularly checkpoint inhibitors like PD-1 and CTLA-4 [132].

In conclusion, the exploration of mitochondrial function in cancer therapy is undergoing rapid advancements. Emerging mitochondrial-targeted therapies are showing promise not only in selectively inducing tumor cell death but also in synergizing with existing therapies to enhance their effectiveness. As we continue to deepen our understanding of mitochondrial roles in cancer biology and therapeutic resistance, we believe that mitochondrial-targeted therapies will become a cornerstone in future cancer treatments, offering more precise, efficient, and individualized treatment options for patients.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: (I)Conception and design: Ming Zhang and Qian Sun; (II)Writing- original draft: Min Zhang, Yuchen Yang, Jiacheng Wu, and Qian Sun; (III)Supervision: Yuchen Yang and Jiacheng Wu; (IV)Writing – review & editing: Min Zhang, Yuchen Yang, Jiacheng Wu, and Qian Sun. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: Not applicable.
Conflict of interest: The author states no conflict of interest.
Research funding: None.
Data availability: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Wasko UN, Jiang J, Dalton TC, Curiel-Garcia A, Edwards AC, Wang Y, et al. Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer. Nature 2024;629:927–36.
2. Martin TD, Patel RS, Cook DR, Choi MY, Patil A, Liang AC, et al. The adaptive immune system is a major driver of selection for tumor suppressor gene inactivation. Science 2021;373:1327–35.
3. Munteanu C, Turti S, Achim L, Muresan R, Souca M, Prifti E, et al. The relationship between circadian rhythm and cancer disease. Int J Mol Sci 2024;25:5846.
4. Li AL, Lian L, Chen XN, Cai WH, Fan XB, Fan YJ, et al. The role of mitochondria in myocardial damage caused by energy metabolism disorders: from mechanisms to therapeutics. Free Radic Biol Med 2023;208:236–51.
5. Musicco C, Signorile A, Pesce V, Loguercio Polosa P, Cormio A. Mitochondria deregulations in cancer offer several potential targets of therapeutic interventions. Int J Mol Sci 2023;24:10420.
6. Patel D, Thankachan S, Abu Fawaz PP, Venkatesh T, Prasada Kabekkodu S, Suresh PS. Deciphering the role of MitomiRs in cancer: a comprehensive review. Mitochondrion 2023;70: 118–30.
7. Srinivasan S, Guha M, Kashina A, Avadhani NG. Mitochondrial dysfunction and mitochondrial dynamics-The cancer connection. Biochim Biophys Acta Bioenerg 2017;1858:602–14.
8. Kopinski PK, Singh LN, Zhang S, Lott MT, Wallace DC. Mitochondrial DNA variation and cancer. Nat Rev Cancer 2021;21:431–45.
9. Funke VLE, Sandmann S, Melcher V, Seggewiss J, Horvath J, Jäger N, et al. Mitochondrial DNA mutations in medulloblastoma. Acta Neuropathol Commun 2023;11:124.
10. Burr SP, Chinnery PF. Origins of tissue and cell-type specificity in mitochondrial DNA (mtDNA) disease. Hum Mol Genet 2024;33: R3–R11.
11. Gonzalez CD, Nissanka N, Van Booven D, Griswold AJ, Moraes CT. Absence of both MGME1 and POLG EXO abolishes mtDNA whereas absence of either creates unique mtDNA duplications. J Biol Chem 2024;300:107128.
12. Ishikawa K, Miyata D, Hattori S, Tani H, Kuriyama T, Wei FY, et al. Accumulation of mitochondrial DNA with a point mutation in tRNALeu(UUR) gene induces brain dysfunction in mice. Pharmacol Res 2024;208:107374.
13. Naini A, Gilkerson R, Shanske S, Pang J. Detection of mitochondrial DNA (mtDNA) mutations. Methods Cell Biol 2019;155:383–400.
14. Smith AL, Whitehall JC, Bradshaw C, Gay D, Robertson F, Blain AP, et al. Age-associated mitochondrial DNA mutations cause metabolic remodelling that contributes to accelerated intestinal tumorigenesis. Nat Cancer 2020;1:976–89.
15. Liu Y, Huang Y, Xu C, An P, Luo Y, Jiao L, et al. Mitochondrial dysfunction and therapeutic perspectives in cardiovascular diseases. Int J Mol Sci 2022;23:16053.
16. Li Y, Sundquist K, Vats S, Hong MG, Wang X, Chen Y, et al. Mitochondrial heteroplasmic shifts reveal a positive selection of breast cancer. J Transl Med 2023;21:696.
17. Dabravolski SA, Nikiforov NG, Zhuravlev AD, Orekhov NA, Grechko AV, Orekhov AN. Role of the mtDNA mutations and mitophagy in inflammaging. Int J Mol Sci 2022;23:1323.
18. Abad E, Lyakhovich A. Movement of mitochondria with mutant DNA through extracellular vesicles helps cancer cells acquire chemoresistance. ChemMedChem 2021;17:e202100642.
19. Hopkins JF, Sabelnykova VY, Weischenfeldt J, Simon R, Aguiar JA, Alkallas R, et al. Mitochondrial mutations drive prostate cancer aggression. Nat Commun 2017;8:656.
20. Luo Y, Ma J, Lu W. The significance of mitochondrial dysfunction in cancer. Int J Mol Sci 2020;21:5598.
21. Huang G, Li H, Zhang H. Abnormal expression of mitochondrial ribosomal proteins and their encoding genes with cell apoptosis and diseases. Int J Mol Sci 2020;21:8879.
22. Nolfi-Donegan D, Braganza A, Shiva S. Mitochondrial electron transport chain: oxidative phosphorylation, oxidant production, and methods of measurement. Redox Biol 2020;37:101674.
23. Chenna S, Koopman WJH, Prehn JHM, Connolly NMC. Mechanisms and mathematical modeling of ROS production by the mitochondrial electron transport chain. Am J Physiol Cell Physiol 2022;323:C69–C83.
24. Zhao RZ, Jiang S, Zhang L, Yu ZB. Mitochondrial electron transport chain, ROS generation and uncoupling. Int J Mol Med 2019;44:3–15. (Review).
25. Mazat JP, Devin A, Ransac S. Modelling mitochondrial ROS production by the respiratory chain. Cell Mol Life Sci 2020;77:455–65.
26. Indo HP, Hawkins CL, Nakanishi I, Matsumoto KI, Matsui H, Suenaga S, et al. Role of mitochondrial reactive oxygen species in the activation of cellular signals, molecules, and function. Handb Exp Pharmacol 2017; 240:439–56.
27. Costa BP, Nassr MT, Diz FM, Fernandes KHA, Antunes GL, Grun LK, et al. Methoxyeugenol regulates the p53/p21 pathway and suppresses human endometrial cancer cell proliferation. J Ethnopharmacol 2021; 267:113645.
28. Erfu C, Li L, Weiting Q, Tao C, Liwei M, Hemin Y, et al. Matrine attenuating cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity through improved mitochondrial membrane potential and activation of mitochondrial respiratory chain Complex I pathway. Biomed Pharmacother 2024;173:116464.
29. Kalpage HA, Wan J, Morse PT, Zurek MP, Turner AA, Khobeir A, et al. Cytochrome c phosphorylation: control of mitochondrial electron transport chain flux and apoptosis. Int J Biochem Cell Biol 2020;121: 105704.
30. Shimizu S, Eguchi Y, Kamiike W, Waguri S, Uchiyama Y, Matsuda H, et al. Bcl-2 blocks loss of mitochondrial membrane potential while ICE inhibitors act at a different step during inhibition of death induced by respiratory chain inhibitors. Oncogene 1996;13:21–9.
31. Xu J, Ji L, Ruan Y, Wan Z, Lin Z, Xia S, et al. UBQLN1 mediates sorafenib resistance through regulating mitochondrial biogenesis and ROS homeostasis by targeting PGC1β in hepatocellular carcinoma. Signal Transduct Targeted Ther 2021;6:190.
32. Cui P, Wei F, Hou J, Su Y, Wang J, Wang S. STAT3 inhibition induced temozolomide-resistant glioblastoma apoptosis via triggering mitochondrial STAT3 translocation and respiratory chain dysfunction. Cell Signal 2020;71:109598.
33. Abukwaik R, Vera-Siguenza E, Tennant D, Spill F. p53 orchestrates cancer metabolism: unveiling strategies to reverse the Warburg effect. Bull Math Biol 2024;86:124.
34. Kooshan Z, Cárdenas-Piedra L, Clements J, Batra J. Glycolysis, the sweet appetite of the tumor microenvironment. Cancer Lett 2024;600: 217156.
35. Alberghina L. The Warburg effect explained: integration of enhanced glycolysis with heterogeneous mitochondria to promote cancer cell proliferation. Int J Mol Sci 2023;24:15787.
36. Martinez-Outschoorn UE, Prisco M, Ertel A, Tsirigos A, Lin Z, Pavlides S, et al. Ketones and lactate increase cancer cell “stemness,” driving recurrence, metastasis and poor clinical outcome in breast cancer:

achieving personalized medicine via Metabolo-Genomics. Cell Cycle 2011;10:1271–86.
37. Feng Y, Zhang X, Zhang S, Xu S, Chen X, Zhou C, et al. PGAM1 promotes glycolytic metabolism and paclitaxel resistance via pyruvic acid production in ovarian cancer cells. Front Biosci 2022;27:262.
38. Chen L, Huang L, Gu Y, Cang W, Sun P, Xiang Y. Lactate-lactylation hands between metabolic reprogramming and immunosuppression. Int J Mol Sci 2022;23:11943.
39. Feng J, Li J, Wu L, Yu Q, Ji J, Wu J, et al. Emerging roles and the regulation of aerobic glycolysis in hepatocellular carcinoma. J Exp Clin Cancer Res 2020;39:126.
40. Chen AN, Luo Y, Yang YH, Fu JT, Geng XM, Shi JP, et al. Lactylation, a novel metabolic reprogramming code: current status and prospects. Front Immunol 2021;12:688910.
41. Li T, Copeland C, Le A. Glutamine metabolism in cancer. Adv Exp Med Biol 2021;1311:17–38.
42. Li T, Le A. Glutamine metabolism in cancer. Adv Exp Med Biol 2018; 1063:13–32.
43. Jin J, Byun JK, Choi YK, Park KG. Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med 2023;55:706–15.
44. Guo J, Fan J, Zhang Y, Li M, Jin Z, Shang Y, et al. Progesterone inhibits endometrial cancer growth by inhibiting glutamine metabolism through ASCT2. Biosci Rep 2024;44. https://doi.org/10.1042/bsr20232035.
45. Liu H, Xue Q, Cai H, Jiang X, Cao G, Chen T, et al. RUNX3-mediated circDYRK1A inhibits glutamine metabolism in gastric cancer by up-regulating microRNA-889-3p-dependent FBXO4. J Transl Med 2022; 20:120.
46. Yang R, Zhang S, Wang L, Chen Y, Chen X, Xia J, et al. Radiation-induced exosomes promote oral squamous cell carcinoma progression via enhancing SLC1A5-glutamine metabolism. J Oral Pathol Med 2024;53: 458–67.
47. Wang H, Tao Y, Han J, Shen J, Mu H, Wang Z, et al. Disrupting YAP1-mediated glutamine metabolism induces synthetic lethality alongside ODC1 inhibition in osteosarcoma. Cell Oncol 2024;47:1845–61.
48. Yokoyama Y, Estok TM, Wild R. Sirpiglenastat (DRP-104) induces antitumor efficacy through direct, broad antagonism of glutamine metabolism and stimulation of the innate and adaptive immune systems. Mol Cancer Therapeut 2022;21:1561–72.
49. Mirveis Z, Patil N, Byrne HJ. Experimental and computational investigation of the kinetic evolution of the glutaminolysis pathway and its interplay with the glycolysis pathway. FEBS Open Bio 2024;14: 1247–63.
50. Ahmed S, Mahony CB, Torres A, Murillo-Saich J, Kemble S, Cedeno M, et al. Dual inhibition of glycolysis and glutaminolysis for synergistic therapy of rheumatoid arthritis. Arthritis Res Ther 2023;25:176.
51. Feng HG, Wu CX, Zhong GC, Gong JP, Miao CM, Xiong B. Integrative analysis reveals that SLC38A1 promotes hepatocellular carcinoma development via PI3K/AKT/mTOR signaling via glutamine mediated energy metabolism. J Cancer Res Clin Oncol 2023;149:15879–98.
52. Liu H, Zhang H, Liu X, Guo W, Liu Q, Chen L, et al. Pancreatic stellate cells exploit Wnt/β-catenin/TCF7-mediated glutamine metabolism to promote pancreatic cancer cells growth. Cancer Lett 2023;555: 216040.
53. Srivastava A, Srivastava P, Mathur S, Abbas S, Rai N, Tiwari S, et al. Lipid metabolism and mitochondria: cross talk in cancer. Curr Drug Targets 2022;23:606–27.
54. Kolodziej F, O'Halloran KD. Re-evaluating the oxidative phenotype: can endurance exercise save the Western world? Antioxidants 2021; 10:609.
55. Vidali S, Aminzadeh S, Lambert B, Rutherford T, Sperl W, Kofler B, et al. Mitochondria: the ketogenic diet–A metabolism-based therapy. Int J Biochem Cell Biol 2015;63:55–9.
56. Liu J, Bai X, Zhang M, Wu S, Xiao J, Zeng X, et al. Energy metabolism: a new target for gastric cancer treatment. Clin Transl Oncol 2024;26: 338–51.
57. Zhou Y, Li Y, Chen G, Guo X, Gao X, Meng J, et al. ACSL1-Mediated fatty acid β-oxidation enhances metastasis and proliferation in endometrial cancer. Front Biosci 2024;29:66.
58. Feng W, Liang J, Xu B, Huang L, Xu Q, Chen D, et al. Fatty acid metabolism affects hepatocellular carcinoma progression via the PPAR-γ signaling pathway and fatty acid β-oxidation. Int Immunopharmacol 2024;141:112917.
59. Zeng K, Li Q, Song G, Chen B, Luo M, Miao J, et al. CPT2-mediated fatty acid oxidation inhibits tumorigenesis and enhances sorafenib sensitivity via the ROS/PPARγ/NF-κB pathway in clear cell renal cell carcinoma. Cell Signal 2023;110:110838.
60. Lu F, Ye M, Shen Y, Xu Y, Hu C, Chen J, et al. Hypoxic tumor-derived exosomal miR-4488 induces macrophage M2 polarization to promote liver metastasis of pancreatic neuroendocrine neoplasm through RTN3/FABP5 mediated fatty acid oxidation. Int J Biol Sci 2024;20:3201–18.
61. Zhao F, Xiao C, Evans KS, Theivanthiran T, DeVito N, Holtzhausen A, et al. Paracrine Wnt5a-β-catenin signaling triggers a metabolic program that drives dendritic cell tolerization. Immunity 2018;48: 147–60.e7.
62. Ahn S, Park JH, Grimm SL, Piyarathna DWB, Samanta T, Putluri V, et al. Metabolomic rewiring promotes endocrine therapy resistance in breast cancer. Cancer Res 2024;84:291–304.
63. Stevens BM, Jones CL, Pollyea DA, Culp-Hill R, D'Alessandro A, Winters A, et al. Fatty acid metabolism underlies venetoclax resistance in acute myeloid leukemia stem cells. Nat Cancer 2020;1:1176–87.
64. Ghanem N, El-Baba C, Araji K, El-Khoury R, Usta J, Darwiche N. The pentose phosphate pathway in cancer: regulation and therapeutic opportunities. Chemotherapy 2021;66:179–91.
65. Cheng C, Wu W, Yu J, Yuan D, Wang Y, Li L. [A novel Chinese medicine formula inhibits non-small cell lung cancer by triggering oxidative stress dependent on pentose phosphate pathway]. Zhongguo Fei Ai Za Zhi 2023;26:639–49. [Article in Chinese].
66. Fuentes-Lemus E, Reyes JS, Figueroa JD, Davies MJ, López-Alarcón C. The enzymes of the oxidative phase of the pentose phosphate pathway as targets of reactive species: consequences for NADPH production. Biochem Soc Trans 2023;51:2173–87.
67. Peng Y, Liu QZ, Xu D, Fu JY, Zhang LX, Qiu L, et al. M_4IDP stimulates ROS elevation through inhibition of mevalonate pathway and pentose phosphate pathway to inhibit colon cancer cells. Biochem Pharmacol 2023;217:115856.
68. Stincone A, Prigione A, Cramer T, Wamelink MM, Campbell K, Cheung E, et al. The return of metabolism: biochemistry and physiology of the pentose phosphate pathway. Biol Rev Camb Phil Soc 2015;90:927–63.
69. Lee MH, Malloy CR, Corbin IR, Li J, Jin ES. Assessing the pentose phosphate pathway using [2, 3-$^{13}C_2$]glucose. NMR Biomed 2019;32: e4096.
70. Ravi D, Beheshti A, Abermil N, Lansigan F, Kinlaw W, Matthan NR, et al. Oncogenic integration of nucleotide metabolism *via* fatty acid synthase in non-hodgkin lymphoma. Front Oncol 2021;11:725137.
71. Zhang Q, Zhang Y, Wang C, Tang H, Ma A, Gao P, et al. Gambogic acid exhibits promising anticancer activity by inhibiting the pentose phosphate pathway in lung cancer mouse model. Phytomedicine 2024;129:155657.

72. Jiang Y, Krantz S, Qin X, Li S, Gunasekara H, Kim YM, et al. Caveolin-1 controls mitochondrial damage and ROS production by regulating fission - fusion dynamics and mitophagy. Redox Biol 2022;52:102304.
73. Kashatus JA, Nascimento A, Myers LJ, Sher A, Byrne FL, Hoehn KL, et al. Erk2 phosphorylation of Drp1 promotes mitochondrial fission and MAPK-driven tumor growth. Mol Cell 2015;57:537–51.
74. Zhao J, Zhang J, Yu M, Xie Y, Huang Y, Wolff DW, et al. Mitochondrial dynamics regulates migration and invasion of breast cancer cells. Oncogene 2013;32:4814–24.
75. Wan YY, Zhang JF, Yang ZJ, Jiang LP, Wei YF, Lai QN, et al. Involvement of Drp1 in hypoxia-induced migration of human glioblastoma U251 cells. Oncol Rep 2014;32:619–26.
76. Yu M, Nguyen ND, Huang Y, Lin D, Fujimoto TN, Molkentine JM, et al. Mitochondrial fusion exploits a therapeutic vulnerability of pancreatic cancer. JCI Insight 2019;5:e126915.
77. Li M, Wang L, Wang Y, Zhang S, Zhou G, Lieshout R, et al. Mitochondrial fusion via OPA1 and MFN1 supports liver tumor cell metabolism and growth. Cells 2020;9:121.
78. Humphries BA, Cutter AC, Buschhaus JM, Chen YC, Qyli T, Palagama DSW, et al. Enhanced mitochondrial fission suppresses signaling and metastasis in triple-negative breast cancer. Breast Cancer Res 2020;22:60.
79. Larrue C, Mouche S, Lin S, Simonetta F, Scheidegger NK, Poulain L, et al. Mitochondrial fusion is a therapeutic vulnerability of acute myeloid leukemia. Leukemia 2023;37:765–75.
80. Jin P, Jiang J, Zhou L, Huang Z, Nice EC, Huang C, et al. Mitochondrial adaptation in cancer drug resistance: prevalence, mechanisms, and management. J Hematol Oncol 2022;15:97.
81. Liu YJ, Fan XY, Zhang DD, Xia YZ, Hu YJ, Jiang FL, et al. Dual inhibition of pyruvate dehydrogenase complex and respiratory chain complex induces apoptosis by a mitochondria-targeted fluorescent organic arsenical *in vitro* and *in vivo*. ChemMedChem 2020;15:552–8.
82. Luo L, Xiong Y, Jiang N, Zhu X, Wang Y, Lv Y, et al. VDAC1 as a target in cisplatin anti-tumor activity through promoting mitochondria fusion. Biochem Biophys Res Commun 2021;560:52–8.
83. Wang H, Shi W, Zeng D, Huang Q, Xie J, Wen H, et al. pH-activated, mitochondria-targeted, and redox-responsive delivery of paclitaxel nanomicelles to overcome drug resistance and suppress metastasis in lung cancer. J Nanobiotechnol 2021;19:152.
84. Guo X, Yang N, Ji W, Zhang H, Dong X, Zhou Z, et al. Mito-bomb: targeting mitochondria for cancer therapy. Adv Mater 2021;33: e2007778.
85. Chen S, Yu S, Du Z, Huang X, He M, Long S, et al. Synthesis of mitochondria-anchored nitroimidazoles with a versatile NIR fluorophore for hypoxic tumor-targeting imaging and chemoradiotherapy. J Med Chem 2021;64:3381–91.
86. Wang Y, Wang W, Gu R, Chen J, Chen Q, Lin T, et al. *In situ* vaccination with mitochondria-targeting immunogenic death inducer elicits $CD8^+$ T cell-dependent antitumor immunity to boost tumor immunotherapy. Adv Sci 2023;10:e2300286.
87. Jiang H, Fu H, Guo Y, Hu P, Shi J. Evoking tumor associated macrophages by mitochondria-targeted magnetothermal immunogenic cell death for cancer immunotherapy. Biomaterials 2022;289:121799.
88. Rinaldi L, Delle Donne R, Borzacchiello D, Insabato L, Feliciello A. The role of compartmentalized signaling pathways in the control of mitochondrial activities in cancer cells. Biochim Biophys Acta Rev Cancer 2018;1869:293–302.
89. Zhao Y, Feng X, Chen Y, Selfridge JE, Gorityala S, Du Z, et al. 5-Fluorouracil enhances the antitumor activity of the glutaminase inhibitor CB-839 against *PIK3CA*-mutant colorectal cancers. Cancer Res 2020;80:4815–27.
90. Qu H, Shan K, Tang C, Cui G, Fu G, Qi Y, et al. A novel small-molecule fatty acid synthase inhibitor with antitumor activity by cell cycle arrest and cell division inhibition. Eur J Med Chem 2021;219:113407.
91. Li Y, Fu J, Hou H, Tang W, Liu Z, Gao D, et al. Chondroitin sulfate-modified antiangiogenic peptide conjugate induces cell apoptosis via the mitochondria-mediated pathway to perform antitumor activity. Int J Biol Macromol 2024;262:129671.
92. Fu X, Mao Q, Zhang B, Lv J, Ping K, Zhang P, et al. Thiazolidinedione-based structure modification of celastrol provides thiazolidinedione-conjugated derivatives as potent agents against non-small-cell lung cancer cells through a mitochondria-mediated apoptotic pathway. J Nat Prod 2022;85:1147–56.
93. Alotaibi AA, Bepari A, Assiri RA, Niazi SK, Nayaka S, Rudrappa M, et al. *Saussurea lappa* exhibits anti-oncogenic effect in hepatocellular carcinoma, HepG2 cancer cell line by bcl-2 mediated apoptotic pathway and mitochondrial cytochrome C release. Curr Issues Mol Biol 2021;43:1114–32.
94. Jin H, Kim HS, Yu ST, Shin SR, Lee SH, Seo GS. Synergistic anticancer effect of docosahexaenoic acid and isoliquiritigenin on human colorectal cancer cells through ROS-mediated regulation of the JNK and cytochrome c release. Mol Biol Rep 2021;48:1171–80.
95. Carobeli LR, Santos ABC, Martins LBM, Damke E, Consolaro MEL. Recent advances in photodynamic therapy combined with chemotherapy for cervical cancer: a systematic review. Expert Rev Anticancer Ther 2024;24:263–82.
96. He F, Li W, Liu B, Zhong Y, Jin Q, Qin X. Progress of piezoelectric semiconductor nanomaterials in sonodynamic cancer therapy. ACS Biomater Sci Eng 2024;10:298–312.
97. Wu Y, Jia C, Liu W, Zhan W, Chen Y, Lu J, et al. Sodium citrate targeting Ca^{2+}/CAMKK2 pathway exhibits anti-tumor activity through inducing apoptosis and ferroptosis in ovarian cancer. J Adv Res 2024;65:89–104.
98. Chen J, Zhang R, Tao C, Huang X, Chen Z, Li X, et al. CuS-NiS_2 nanomaterials for MRI guided phototherapy of gastric carcinoma *via* triggering mitochondria-mediated apoptosis and MLKL/CAPG-mediated necroptosis. Nanotoxicology 2020;14:774–87.
99. Buchke S, Sharma M, Bora A, Relekar M, Bhanu P, Kumar J. Mitochondria-targeted, nanoparticle-based drug-delivery systems: therapeutics for mitochondrial disorders. Life 2022;12:657.
100. Mironov VF, Dimukhametov MN, Nemtarev AV, Pashirova TN, Tsepaeva OV, Voloshina AD, et al. Novel mitochondria-targeted amphiphilic aminophosphonium salts and lipids nanoparticles: synthesis, antitumor activity and toxicity. Nanomaterials 2023;13:2840.
101. Biswas S, Dodwadkar NS, Deshpande PP, Torchilin VP. Liposomes loaded with paclitaxel and modified with novel triphenylphosphonium-PEG-PE conjugate possess low toxicity, target mitochondria and demonstrate enhanced antitumor effects *in vitro* and *in vivo*. J Contr Release 2012;159:393–402.
102. Cho H, Cho YY, Shim MS, Lee JY, Lee HS, Kang HC. Mitochondria-targeted drug delivery in cancers. Biochim Biophys Acta Mol Basis Dis 2020;1866:165808.
103. Tabish TA, Hamblin MR. Mitochondria-targeted nanoparticles (mitoNANO): an emerging therapeutic shortcut for cancer. Biomater Biosyst 2021;3:100023.
104. Grazioli S, Pugin J. Mitochondrial damage-associated molecular patterns: from inflammatory signaling to human diseases. Front Immunol 2018;9:832.
105. Faas MM, De Vos P. Mitochondrial function in immune cells in health and disease. Biochim Biophys Acta Mol Basis Dis 2020;1866:165845.

106. Liu Y, Yan W, Tohme S, Chen M, Fu Y, Tian D, et al. Hypoxia induced HMGB1 and mitochondrial DNA interactions mediate tumor growth in hepatocellular carcinoma through Toll-like receptor 9. J Hepatol 2015; 63:114–21.
107. Li J, Huynh L, Cornwell WD, Tang MS, Simborio H, Huang J, et al. Electronic cigarettes induce mitochondrial DNA damage and trigger TLR9 (Toll-Like receptor 9)-mediated atherosclerosis. Arterioscler Thromb Vasc Biol 2021;41:839–53.
108. Mekala N, Trivedi J, Bhoj P, Togre N, Rom S, Sriram U, et al. Alcohol and e-cigarette damage alveolar-epithelial barrier by activation of P2X7r and provoke brain endothelial injury via extracellular vesicles. Cell Commun Signal 2024;22:39.
109. Banoth B, Cassel SL. Mitochondria in innate immune signaling. Transl Res 2018;202:52–68.
110. Leite-Aguiar R, Bello-Santos VG, Castro NG, Coutinho-Silva R, Savio LEB. Techniques for evaluating the ATP-gated ion channel P2X7 receptor function in macrophages and microglial cells. J Immunol Methods 2024;532:113727.
111. Luo M, Wang X, Wu S, Yang C, Su Q, Huang L, et al. A20 promotes colorectal cancer immune evasion by upregulating STC1 expression to block “eat-me” signal. Signal Transduct Targeted Ther 2023;8:312.
112. Cui X, Yao A, Jia L. Starvation insult induces the translocation of high mobility group box 1 to cytosolic compartments in glioma. Oncol Rep 2023;50:216.
113. Lu RO, Ho WS. Mitochondrial dysfunction, macrophage, and microglia in brain cancer. Front Cell Dev Biol 2021;8:620788.
114. Zhang H, Yu X, Ye J, Li H, Hu J, Tan Y, et al. Systematic investigation of mitochondrial transfer between cancer cells and T cells at single-cell resolution. Cancer Cell 2023;41:1788–802.e10.
115. Scharping NE, Rivadeneira DB, Menk AV, Vignali PDA, Ford BR, Rittenhouse NL, et al. Mitochondrial stress induced by continuous stimulation under hypoxia rapidly drives T cell exhaustion. Nat Immunol 2021;22:205–15.
116. Song BS, Moon JS, Tian J, Lee HY, Sim BC, Kim SH, et al. Mitoribosomal defects aggravate liver cancer via aberrant glycolytic flux and T cell exhaustion. J Immunother Cancer 2022;10:e004337.
117. Shen H, Chang Y, Lu W, Xu H, Wang S, Ma J. [Lewis tumor cell conditioned medium enhances immunosuppressive function of mouse myeloid-derived suppressor cells by regulating glycolytic pathway]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2019;35:491–7. [Article in Chinese].
118. Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S, et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. Nature 2021;591:645–51.
119. Xu W, Ghosh S, Comhair SA, Asosingh K, Janocha AJ, Mavrakis DA, et al. Increased mitochondrial arginine metabolism supports bioenergetics in asthma. J Clin Investig 2016;126:2465–81.
120. Martí i Líndez AA, Dunand-Sauthier I, Conti M, Gobet F, Núñez N, Hannich JT, et al. Mitochondrial arginase-2 is a cell-autonomous regulator of CD8+ T cell function and antitumor efficacy. JCI Insight 2019;4:e132975.
121. Dubey S, Ghosh S, Goswami D, Ghatak D, De R. Immunometabolic attributes and mitochondria-associated signaling of Tumor-Associated Macrophages in tumor microenvironment modulate cancer progression. Biochem Pharmacol 2023;208:115369.
122. Hossenipour Khodaei S, Sabetnam S, Nozad Charoudeh H, Dizaji Asl K, Rafat A, Mazloumi Z. The effect of mitochondria inhibition on natural killer cells cytotoxicity in triple-negative breast cancer cells. Eur J Pharmacol 2023;960:176106.
123. Minhas PS, Liu L, Moon PK, Joshi AU, Dove C, Mhatre S, et al. Macrophage de novo NAD+ synthesis specifies immune function in aging and inflammation. Nat Immunol 2019;20:50–63.
124. Navas LE, Carnero A. NAD+ metabolism, stemness, the immune response, and cancer. Signal Transduct Targeted Ther 2021;6:2.
125. Li W, Liang L, Liao Q, Li Y, Zhou Y. CD38: an important regulator of T cell function. Biomed Pharmacother 2022;153:113395.
126. Zheng Z, Bian Y, Zhang Y, Ren G, Li G. Metformin activates AMPK/SIRT1/NF-κB pathway and induces mitochondrial dysfunction to drive caspase3/GSDME-mediated cancer cell pyroptosis. Cell Cycle 2020;19: 1089–104.
127. Roboon J, Hattori T, Ishii H, Takarada-Iemata M, Nguyen DT, Heer CD, et al. Inhibition of CD38 and supplementation of nicotinamide riboside ameliorate lipopolysaccharide-induced microglial and astrocytic neuroinflammation by increasing NAD. J Neurochem 2021; 158:311–27.
128. Chatterjee S, Daenthanasanmak A, Chakraborty P, Wyatt MW, Dhar P, Selvam SP, et al. CD38-NAD+Axis regulates immunotherapeutic anti-tumor T cell response. Cell Metab 2018;27:85–100.e8.
129. Hogan KA, Chini CCS, Chini EN. The multi-faceted ecto-enzyme CD38: roles in immunomodulation, cancer, aging, and metabolic diseases. Front Immunol 2019;10:1187.
130. Siddiqui RA, Shaikh SR, Sech LA, Yount HR, Stillwell W, Zaloga GP. Omega 3-fatty acids: health benefits and cellular mechanisms of action. Mini Rev Med Chem 2004;4:859–71.
131. Liu S, Tian H, Ming H, Zhang T, Gao Y, Liu R, et al. Mitochondrial-targeted CS@KET/P780 nanoplatform for site-specific delivery and high-efficiency cancer immunotherapy in hepatocellular carcinoma. Adv Sci 2024;11:e2308027.
132. Chowdhury PS, Chamoto K, Kumar A, Honjo T. PPAR-induced fatty acid oxidation in T cells increases the number of tumor-reactive $CD8^+$ T cells and facilitates anti-PD-1 therapy. Cancer Immunol Res 2018;6: 1375–87.
133. Rad SMAH, Halpin JC, Mollaei M, Smith Bell SWJ, Hirankarn N, McLellan AD. Metabolic and mitochondrial functioning in chimeric antigen receptor (CAR)-T cells. Cancers 2021;13:1229.
134. Ren L, Wan J, Li X, Yao J, Ma Y, Meng F, et al. Mitochondrial rewiring with small-molecule drug-free nanoassemblies unleashes anticancer immunity. Nat Commun 2024;15:7664.
135. Tsuji A, Akao T, Masuya T, Murai M, Miyoshi H. IACS-010759, a potent inhibitor of glycolysis-deficient hypoxic tumor cells, inhibits mitochondrial respiratory complex I through a unique mechanism. J Biol Chem 2020;295:7481–91.
136. Yap TA, Daver N, Mahendra M, Zhang J, Kamiya-Matsuoka C, Meric-Bernstam F, et al. Complex I inhibitor of oxidative phosphorylation in advanced solid tumors and acute myeloid leukemia: phase I trials. Nat Med 2023;29:115–26.
137. Yu F, Li X, Sheng C, Li L. DNA nanotechnology targeting mitochondria: from subcellular molecular imaging to tailor-made therapeutics. Angew Chem Int Ed Engl 2024;63:e202409351.
138. Zinovkina LA, Makievskaya CI, Galkin II, Zinovkin RA. Mitochondria-targeted uncouplers decrease inflammatory reactions in endothelial cells by enhancing methylation of the ICAM1 gene promoter. Curr Mol Pharmacol 2024;17. https://doi.org/10.2174/1874467217666230815142556.
139. Su Y, Tu Y, Lin H, Wang MM, Zhang GD, Yang J, et al. Mitochondria-targeted Pt(IV) prodrugs conjugated with an aggregation-induced emission luminogen against breast cancer cells by dual modulation of apoptosis and autophagy inhibition. J Inorg Biochem 2022;226:111653.

140. Zhang YM, Xia M, Ao R, Gao LX, Tang Y, Huang JH, et al. Smart design of mitochondria-targeted and ROS-responsive CPI-613 delivery nanoplatform for bioenergetic pancreatic cancer therapy. Nanomaterials 2021;11:2875.
141. Zacharioudakis E, Gavathiotis E. Mitochondrial dynamics proteins as emerging drug targets. Trends Pharmacol Sci 2023;44: 112–27.
142. Falone S, Lisanti MP, Domenicotti C. Oxidative stress and reprogramming of mitochondrial function and dynamics as targets to modulate cancer cell behavior and chemoresistance. Oxid Med Cell Longev 2019;2019:4647807–4.
143. Yang Y, Karakhanova S, Hartwig W, D'Haese JG, Philippov PP, Werner J, et al. Mitochondria and mitochondrial ROS in cancer: novel targets for anticancer therapy. J Cell Physiol 2016;231:2570–81.