Mitochondria in T-cell tumor immunity and tumor therapies targeting mitochondria (Review)

MINJIE ZHOU, YIJIE XIE, ZHIPENG LIU, YI HE, YIBING YIN, KEYU CHEN, ZHENGYU ZHAO, CHENGSHUN ZHANG and DINGJUN CAI

Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, P.R. China

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Abstract. Mitochondria are central to cellular metabolic reprogramming, and their energy metabolism pathways are indispensable for T-cell activation, proliferation and differentiation. Mitochondrial metabolic reprogramming enhances T-cell activity and antitumor function. Mitochondrial dynamics, including fusion, fission and transfer, regulate T-cell tumor immune function by modulating the number, morphology and distribution of mitochondria, which is vital for the antitumor effects of T cells. The release of mitochondrial DNA can activate multiple innate immune signaling pathways, such as cyclic GMP-AMP synthase-stimulator of interferon genes, Toll-like receptor 9, and NOD-, LRR-, and pyrin domain-containing protein 3, serving a complex regulatory role in shaping the tumor immunosuppressive microenvironment and T-cell antitumor immune responses. Notably, mitochondrial dysfunction is a major driver of tumor initiation and progression. T-cell mitochondrial metabolic reprogramming, dynamic changes and mitochondrial DNA release all affect the antitumor immunity of tumor-infiltrating T cells. The present review focuses on the relationship between mitochondria and T-cell antitumor immune responses, exploring the core role of mitochondria in T-cell tumor immunity from multiple aspects, including mitochondrial energy metabolism, mitochondrial dynamics and mitochondrial DNA. In addition, the present review examines state-of-the-art research on antitumor therapies targeting mitochondria from multiple perspectives, with the aim of providing a reference for developing mitochondria-targeted antitumor immunotherapy strategies.

Correspondence to: Professor Dingjun Cai, Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, 1166 Liutai Avenue, Wenjiang, Chengdu, Sichuan 611137, P.R. China
E-mail: djcai@cdutcm.edu.cn

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Contents

1. Introduction

Mitochondria, as highly dynamic organelles with various biological functions within cells (1,2), serve a crucial regulatory role in metabolic regulation and the activation of immune cells (3). As the center of cellular energy metabolism and biosynthesis, mitochondria produce ATP through oxidative phosphorylation (OXPHOS) to maintain cellular energy homeostasis (4). The regulation of mitochondrial dynamics is notably associated with tumor cell proliferation and migration, as well as treatment outcomes (5). Mitochondrial release of mitochondrial DNA (mtDNA), mitochondrial reactive oxygen species (mtROS) and metabolites is involved in the regulation of various cellular biological processes, including energy metabolism and immune responses (6). Dynamic changes in mitochondrial fusion and fission affect their metabolic function, and, in turn, the metabolic state regulates the dynamic equilibrium of mitochondria. This bidirectional interaction influences the metabolism and effector functions of T cells (7). mtDNA mutations or damage can affect mitochondrial function, including metabolic efficiency and dynamic behavior, thereby directly impacting T-cell capability (8). In addition, the metabolic state of mitochondria can regulate mitochondrial dynamics and mtDNA through pathways such as mTOR and AMPK (9). Increasing evidence has indicated that mitochondrial dysfunction is associated with the occurrence of various diseases, including autoimmune diseases and tumors (10-12).

To ensure normal mitochondrial structure, function and quantity, cells have evolved a sophisticated mitochondrial quality control system that can repair mildly damaged mitochondria or isolate severely damaged ones through mitochondrial dynamics. This system can actuate mitochondrial

degradation and renewal through mitophagy and biogenesis, ultimately maintaining mitochondrial homeostasis to meet cellular metabolic needs (13).

In the tumor microenvironment (TME), tumor cells drive nutrient depletion and excessive production of metabolic byproducts, modulating the metabolic reprogramming of infiltrating immune cells and the activation of related signaling pathways, such as the AMPK signaling axis and the mTOR signaling pathway. These pathways control the polarization of different types of immune cells, inducing metabolic dysregulation that leads to the loss of antitumor immune responses (14,15). Hypoxia and continuous antigen stimulation are common forms of metabolic stress manifested in the TME. Prolonged exposure to low-oxygen conditions induces mitochondrial stress leading to elevated ROS levels (16), which rapidly causes the exhaustion of tumor-infiltrating $CD8^+$ T cells and mitochondrial damage or depolarization (17). This results in the metabolic exhaustion and functional decline of $CD8^+$ tumor-infiltrating lymphocytes (TILs), facilitating tumor immune evasion (18).

The present review explores the relationship between mitochondria and T-cell antitumor immune responses, investigating the key regulatory roles of mitochondrial dynamics, energy metabolism and mtDNA in tumor occurrence, development and immune evasion. The current review aims to provide a deeper understanding of the regulatory mechanisms by which mitochondria influence T cells during tumor development. Additionally, antitumor interventions targeting mitochondria are discussed, providing a basis for developing mitochondrial-targeted antitumor immunotherapy strategies.

2. Structure and function of T cells in the TME

Mitochondria within T cells have complex structures, including an outer membrane, inner membrane, intermembrane space and matrix (19). The outer membrane contains selective ion channels and membrane proteins that regulate intercellular communication (20). The intermembrane space is involved in protein and lipid biosynthesis, and redox regulation. The inner membrane folds to form cristae housing the electron transport chain and respiratory enzyme complexes (21). The matrix is the site of the tricarboxylic acid (TCA) cycle, providing substrates for OXPHOS and regulating various metabolites. In addition to energy supply, mitochondria influence $CD8^+$ T-cell activation, signal transduction and cytotoxicity through regulation of ROS production and calcium ion (Ca^{2+}) balance (22).

The TME refers to the dynamic environment surrounding the tumor, serving as the 'soil' for tumor cell proliferation. Tumor cells can control tumor-associated antigen (TAA) expression, enhance the expression of immune checkpoint molecules, secrete immunosuppressive cytokines and accumulate lactic acid metabolites, altering the metabolic status, TAA recognition ability and tumor-killing potency of infiltrating immune cells (23). This creates an immunosuppressive microenvironment favorable for tumor growth and spread.

As the tumor progresses, factors such as reduced oxygen content, increased ROS production, depolarized membrane potential and nutrient deprivation in the TME disrupt T-cell mitochondrial metabolism and impair their function (24-26), manifesting as poor mitochondrial adaptability, reduced abundance, decreased or lost membrane potential, dynamic imbalance, reduced cristae number, and disordered shape and arrangement. These factors can lead to dysfunction of the TCA cycle and OXPHOS, electron transport chain dysfunction decreased ATP synthesis efficiency and excessive ROS production (27). However, mitophagy, as a core mechanism of mitochondrial quality control, promptly removes dysfunctional mitochondria, preventing excessive ROS accumulation, mtDNA leakage and T-cell apoptosis, while maintaining OXPHOS efficiency through mitochondrial renewal, thereby providing ATP for T-cell proliferation and effector functions (28,29).

3. Mitochondrial metabolism and tumor immunity of T cells

Role of mitochondrial metabolism in T-cell activation, proliferation and effector functions. As the energy and metabolic centers of the cell, mitochondria provide energy through regulating metabolic pathways such as the TCA cycle, OXPHOS and fatty acid oxidation (FAO). Mitochondrial metabolism supplies sufficient ATP to meet the energy demands of cell division and growth. Furthermore, biosynthetic precursor substances produced by glycolysis and fatty acid synthesis (FAS), such as glucose-6-phosphate and pyruvate, are used for the synthesis of nucleic acids, proteins and lipids (30).

During T-cell activation and proliferation, mitochondrial metabolic patterns change. The mitochondria of naïve T cells are often fragmented, relying predominantly on mitochondrial OXPHOS and FAO to maintain energy requirements in a resting state (31). Through regulating the surface expression of GLUT1, which is required for basal glucose uptake, metabolic homeostasis is maintained, thereby promoting OXPHOS (32). Mitochondrial pyruvate carrier 1 (MPC1) promotes mitochondrial uptake and oxidation of pyruvate, which is crucial for the development and maturation of T cells in the thymus (33). Within the first 24 h of T-cell activation, the mitochondrial proteome undergoes notable restructuring, enhancing mitochondrial one-carbon metabolism to support rapid T-cell activation (34). Stomatin like protein-2forms microdomains in mitochondria and cell membranes, promoting membrane regionalization and assembly of the T-cell receptor (TCR) signaling complex, thereby enhancing T-cell activation (35).

Upon T-cell activation, mitochondria undergo morphological changes, transforming from a fragmented state into longer, more fused forms. Activated T cells exhibit marked increases in OXPHOS, the TCA cycle and FAS to maintain their effector functions (36). When T cells recognize antigens, they transition from a resting state to an activated state, characterized predominantly by proliferation, survival and differentiation, which drive the initiation of the cell cycle, cell growth, IL-2 signaling and enhanced metabolic flux to sustain anabolic metabolism (37). TCR signals, co-stimulatory signals and cytokines are necessary conditions for full activation of T cells, with activation levels assessed by proliferation capacity, cytokine secretion, effector performance and differentiation state, all requiring enhanced anabolic metabolism to provide the necessary energy and material base (38,39). When TCR and co-receptors recognize the antigen peptide-major histocompatibility complex (MHC) (signal 1) and receive

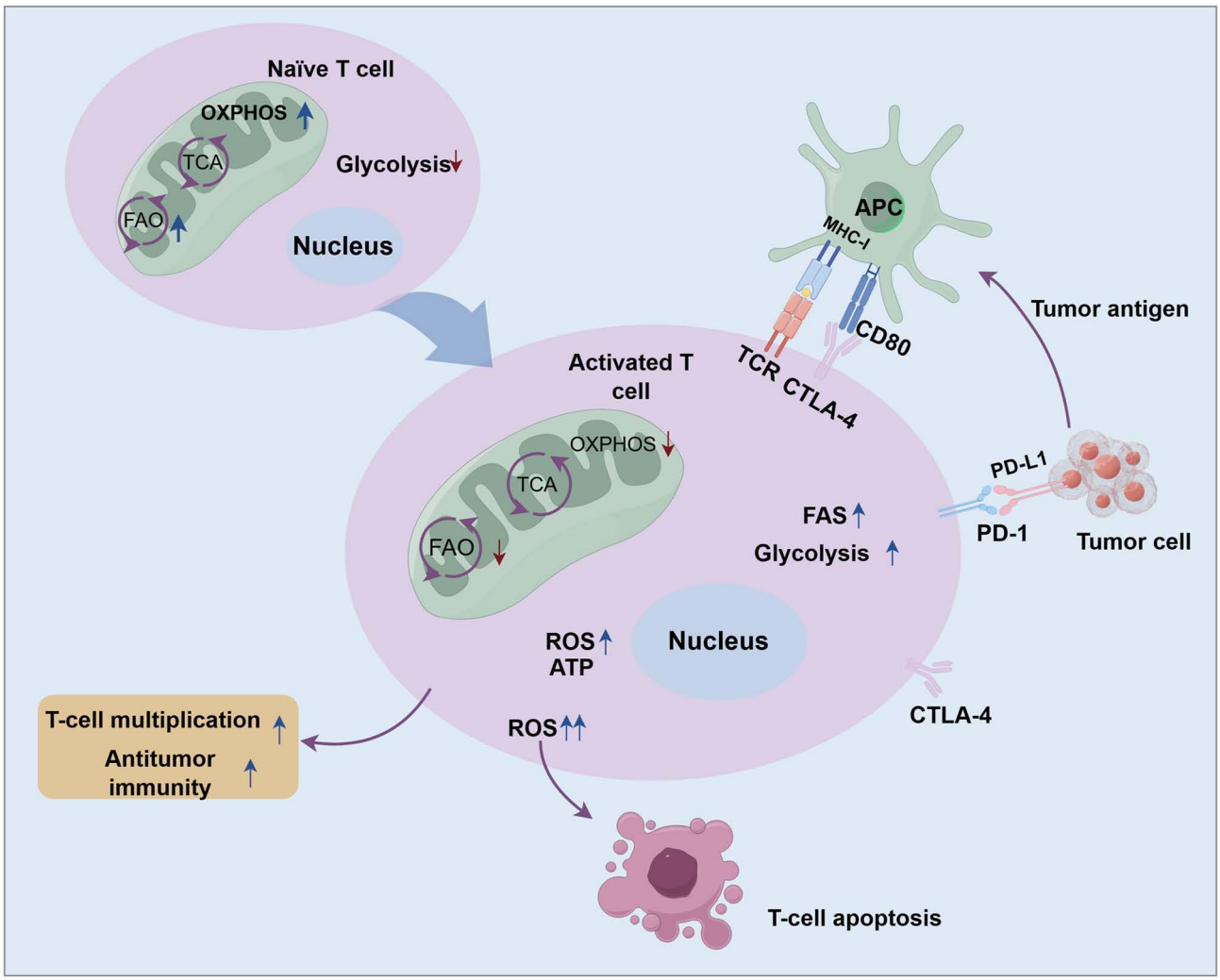

Figure 1. Mitochondrial metabolic reprogramming-mediated T-cell activation. Through regulation of T-cell proliferation, activation and differentiation, mitochondrial metabolic reprogramming enhances antitumor immunity by boosting immune cell-mediated tumor killing and surveillance. APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FAO, fatty acid oxidation; FAS, fatty acid synthesis; MHC, major histocompatibility complex; OXPHOS, oxidative phosphorylation; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; TCA, tricarboxylic acid; TCR, T-cell receptor.

co-stimulation (signal 2), it triggers phosphorylation signals such as PI3K/AKT, activating mTOR complex 1 (mTORC1) and transcription factors, such as NFAT and MYC in activated T cells, thereby regulating the expression of key enzymes in glycolysis and mitochondrial anabolic metabolism (40,41). In early T-cell activation before cell division, enhanced glycolytic flux and mitochondrial respiration occur. This process takes place in mature immune synapses (ISs) lasting several hours, providing a platform for repeated transmission of T-cell signals (42,43).

Memory $CD8^+$ T cells exhibit long-term survival in the body through FAO; upon re-encountering the same antigen, mitochondrial metabolism involving FAO and OXPHOS is increased to support the rapid proliferation of memory T cells, and mitochondrial morphology transforms from fragmented to fused, with tightly packed cristae and higher metabolic efficiency. Exhausted T cells exhibit decreased mitochondrial quality and function, reduced glucose uptake, and lowered levels of glycolysis and OXPHOS (44). Some T cells enhance FAO by increasing AMPK activity or inhibiting mTOR to participate in the transition from an effector to a memory state (45). T-cell activation is illustrated in Fig. 1.

Spatial heterogeneity. Tumor immune niches, tertiary lymphoid structures (TLSs) and tumor-draining lymph nodes (TDLNs) are key sites of intercellular communication (46,47); notably, interest has been garnered in spatial determinants that regulate $CD8^+$ T-cell function in these locations. TDLNs naturally serve as reservoirs for tumor-specific $CD8^+$ TILs. Extensive research has provided evidence of $CD8^+$ T cells migrating from TDLNs to the tumor, demonstrating that tumor-specific $CD8^+$ T cells activated in TDLNs generally exist in a minimally exhausted precursor-exhausted T cell (Tpex) or Tpex-like state, whereas their clone-related TILs predominantly exhibit an exhausted terminally differentiated T-cell phenotype (48-51).

Within the TME, the localization, distribution patterns and anatomical positions of $CD8^+$ T cells markedly affect their functional state, differentiation fate and antitumor efficacy (52). Studies have demonstrated that the spatial positioning of $CD8^+$ T cells determines functional subtypes, and the Immunoscore

system can be used to quantify $CD8^+$ T-cell density in the tumor core and invasive margin region, in order to predict prognosis (53-55). Unlike traditional memory-like differentiation, $CD8^+$ T-cell subtypes in the TME show that Tpex cells share certain stem-like characteristics with memory T cells (such as TCF1 expression); however, their terminal exhaustion state is difficult to reverse due to epigenetic reprogramming and persistent antigen exposure (56).

Metabolic heterogeneity appears to contribute to the heterogeneity of the tumor immune microenvironment. Hypoxic zones at the tumor core inhibit the mitochondrial respiratory chain through hypoxia-inducible factor (HIF)-1α, leading to TIL metabolic reprogramming towards inefficient glycolysis, inhibiting mitochondrial biogenesis and resulting in functional exhaustion (57). Conversely, in oxygen-rich perivascular regions, TILs retain OXPHOS capabilities, maintaining stem-like characteristics. Malignant cells with high glycolytic activity can transform their metabolic pathways into anabolic reactions (58), producing large amounts of immunosuppressive mediators, such as lactate and adenosine, inhibiting mitochondrial function, and weakening TIL survival and cytotoxic functions (59,60).

TLSs are often located near blood vessels (61), where expression of mitochondrial biogenesis markers is markedly higher compared with in non-TLS region TILs. Perivascular TIL subtypes have unique metabolic adaptability, and spatially, TILs located around blood vessels exhibit lower concentrations of inhibitors such as lactate, adenosine and ROS compared with those in the tumor core. Glucose, glutamine and oxygen concentrations are close to normal tissue levels, supporting aerobic mitochondrial metabolism of TILs (62), with mitochondrial structures and functions being more intact. Mitochondrial metabolites serve as substrates for epigenetic modifications, with spatial microenvironment differences leading to diverse histone acetylation/methylation patterns in TILs, affecting TIL exhaustion or transition into memory cells (63). Enhancing MPC-dependent OXPHOS through the IL-10-Fc fusion protein can reprogram terminally exhausted T-cell metabolism, restoring some function (64). In summary, TLSs can construct blood vessel-associated metabolic zones, allowing internal TILs to avoid tumor metabolic inhibition, maintain mitochondrial function and epigenetic plasticity, becoming functional response pools for immunotherapy.

Mitochondrial metabolism and tumor immunity in T cells. Mitochondrial functions and metabolic pathways undergo metabolic reprogramming to adapt to cellular environments or states (35). Mitochondrial metabolic reprogramming can enhance the antitumor activity and immune response of T cells, serving a critical role in the antitumor activity of T cells infiltrating the TME (65).

Continuous stimulation of T cells in hypoxic environments can lead to Blimp-1-mediated peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α)-dependent mitochondrial reprogramming inhibition, resulting in persistent loss of mitochondrial function and quality (66). Notably, upregulation of PGC-1α enhances mitochondrial biogenesis and metabolic abilities, boosting the antitumor effects of $CD8^+$ T cells (67). In glucose-deficient TMEs, activation of the endoplasmic reticulum (ER) to nucleus signaling 1α-X-box binding protein 1 signaling axis inhibits the abundance of glutamine transporters in T cells, limiting the availability of glutamine crucial for maintaining mitochondrial respiration and leading to reduced T-cell antitumor function (68). Additionally, under glucose-restricted conditions, T cells suppress signaling pathways via the mTORC1 pathway, reducing the expression of antigen-induced genes, and weakening $CD8^+$ T-cell adhesion, proliferation capacity and their ability to secrete cytokines, such as IFN-γ, granulocyte-macrophage colony-stimulating factor and granzyme B (36,69).

MPC deficiency hampers mitochondrial oxidation of lactate, impairing $CD8^+$ T-cell antitumor effector functions (70). The half-life-extended leukocyte IL-10-Fc fusion protein enhances the proliferation and cytotoxic function of terminally exhausted $CD8^+$ T cells by upregulating MPC-dependent OXPHOS metabolism, thereby improving the antitumor efficacy of immunotherapy (64). Linoleic acid enhances ER-mitochondria contacts in $CD8^+$ T cells, promoting Ca^{2+} signaling and mitochondrial energy metabolism, maintaining metabolic balance (71); this enables secretion of more cytokines such as granzyme B and perforin, enhancing their cytotoxic capability (72), thereby bolstering $CD8^+$ T-cell activity and antitumor capacity in the TME. Therefore, mitochondrial metabolic reprogramming can enhance the antitumor activity and immune response of T cells.

Mitochondrial metabolism and immune checkpoint expression in T cells. Immune checkpoints are a class of immunosuppressive molecules that regulate the degree of immune activation to prevent overly activated T cells from damaging normal tissues. Programmed death-1 (PD-)1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are common immune checkpoints, which have notable immunoregulatory roles under normal circumstances. When programmed death-ligand 1 (PD-L1) is highly expressed on tumor cells and binds with PD-1 receptors on T cells, it transmits negative regulatory signals to inhibit TCR signaling and CD28-mediated co-stimulatory signals, leading to T-cell exhaustion and loss of immune response, promoting tumor immune escape (73). The costimulatory molecule CTLA-4 on T cells binds with B7 molecules on antigen-presenting cells (APCs), suppressing T-cell proliferation and activation, as well as antitumor cell capabilities, promoting tumor immune escape (74).

The expression level of immune checkpoint molecules can influence T-cell differentiation and function by affecting mitochondrial structure, function and metabolism. Mitochondrial structural changes occur in response to immune checkpoint molecules, with PD-1 stimulation leading to a reduction in the number and length of mitochondrial cristae (75). When PD-1 binds to PD-L1, it phosphorylates the immunoreceptor tyrosine-based switch motif and immunoreceptor tyrosine-based inhibitory motif on the PD-1 tail, recruiting the SHP2 phosphatase, which inhibits the Ras/MAPK and PI3K/AKT/mTOR glycolytic regulatory pathways critical for T-cell activation. This reduces the glycolytic capacity of T cells, weakening their proliferation and activation functions (76,77). As well as inhibiting T-cell glycolysis, the PD-1/PD-L1 pathway can upregulate the expression of adipose triglyceride lipase and carnitine palmitoyltransferase 1A (CPT1A), promoting endogenous lipid FAO. This shift enables T cells to utilize

fatty acid metabolism for sustained survival, thereby delaying T-cell exhaustion (75). Furthermore, PD-1 signaling phosphorylates STAT3, promoting the expression of CPT1B, a key rate-limiting enzyme in FAO, which accelerates fatty acid catabolism, and inhibits the glycolytic process and functions of $CD8^+$ T effector cells.

When tumor cell-secreted PD-L1 exosomes bind to T-cell PD-1, they activate the CREB and STAT signaling pathways, upregulating cholesterol and phospholipid synthases, promoting lipid metabolism, and accelerating T-cell aging (78,79). In lung cancer, PD-1 on $CD8^+$ T cells inhibits the AKT signaling pathway, promoting the nuclear translocation of the transcription factor GATA1, which inhibits the transcription of phospholipid phosphatase 1. This leads to abnormal phospholipid metabolism, converting unsaturated fatty acids in the TME to unsaturated phospholipids, inducing ferroptosis in $CD8^+$ T cells, reducing cytokine secretion and weakening the antitumor immune response (80).

Mitophagy and ROS in T-cell tumor immunity. Mitophagy is the selective degradation of damaged or dysfunctional mitochondria by cells to maintain homeostasis. There are two main mechanisms of mitophagy: One is the ubiquitin pathway mediated by the Parkin-PINK1 signaling cascade, and the other is the receptor-dependent pathway mediated by BNIP3 and NIX. The Parkin-PINK1 pathway facilitates degradation by adding ubiquitin chains on the surface of damaged mitochondria (81), whereas NIX or BNIP3 are expressed on the mitochondrial surface, and directly recruit and assemble autophagosomes upon mitochondrial damage (82). In healthy mitochondria, PINK1 is constantly cleaved and degraded (83); when mitochondria are depolarized or damaged, PINK1 stabilizes on the outer mitochondrial membrane (OMM) and phosphorylates, recruiting the E3 ubiquitin ligase Parkin. Parkin catalyzes the formation of multiple types of ubiquitin chains on OMM proteins, such as mitofusin (MFN)1/2 and voltage-dependent anion channel (VDAC) (84). By clearing damaged mitochondria, mitophagy suppresses the production of IFN-1 and the activation of inflammasomes, thereby reducing the secretion of IL-1β and IL-18, and preventing the accumulation of mitochondria-derived damage-associated molecular patterns such as ROS and mtDNA (85). BNIP3 can interact with PINK1 to facilitate its stabilization and regulate the recruitment of Parkin. NIX can act as a Parkin substrate, enhancing the recruitment of autophagic adapter proteins via Parkin-mediated ubiquitination, thereby accelerating clearance.

Mitochondria are the primary organelles for intracellular production of ROS through the electron transport chain and OXPHOS process in aerobic respiration (86). The level and sustained generation capacity of ROS serve a crucial role in the antitumor immunity of T cells (87,88). In tumor immunity, activated T cells achieve tumor cell killing by increasing ROS production, recruiting neutrophils and macrophages (89). Extracellular ROS can also affect T-cell activation by altering the immunogenicity of antigen peptides in APCs (90).

Excessive ROS can cause damage to nuclear and mtDNA, and oxidative damage to proteins and lipids, leading to cellular damage (91). It promotes T-cell apoptosis by upregulating pro-apoptotic factors such as Fas and downregulating the expression of the anti-apoptotic protein Bcl-2 (92). Elevated ROS can further promote the transformation of immunosuppressive cells, such as myeloid-derived suppressor cells, tumor-activated macrophages and regulatory T cells, through various pathways, including HIF-1α (93), supporting tumor cell proliferation (91,94). Targeted removal of tumor extracellular ROS can increase T-lymphocyte tumor infiltration, restoring T-cell antitumor immunity induced by immunogenic cell death (95). Additionally, the deficiency of reduced glutathione in regulatory T cells can lead to serine metabolism abnormalities and downregulation of the transcriptional regulator Foxp3 expression, ultimately weakening the immunosuppressive function of regulatory T cells (96).

4. Mitochondrial dynamics in regulating tumor immunity of T cells

Mitochondrial dynamics refer to the continuous processes of fission and fusion, transfer and positioning within cells under physiological or stimulated states, regulating the dynamic equilibrium of mitochondrial distribution, quantity, size and shape within cells (97). The synergistic interactions and balance between mitochondrial dynamics are important for maintaining mitochondrial adaptation to varying metabolic demands and stress environments.

Mitochondrial fusion. Mitochondrial fusion is the process whereby two mitochondria merge into a single organelle, undergoing morphological changes in response to cellular energy demands and the need for material exchange between mitochondria. Proteins involved in mitochondrial fusion in mammalian cells include MFN1, MFN2 and optic atrophy 1 protein (OPA1). MFN1 and MFN2 primarily mediate the fusion of the mitochondrial outer membrane, whereas OPA1 is involved in the inner membrane fusion process. Additionally, MFN2 is located on the ER membrane, mediating physical contact between the ER and mitochondria, and Ca^{2+} homeostasis (98).

During the process of T-cell expansion, mitochondrial fusion prompts a metabolic shift in T cells from glycolysis to FAO and OXPHOS, facilitating the differentiation of naïve T cells into memory phenotypes and enhancing antitumor persistence (99). By regulating Ca^{2+} homeostasis and ROS levels, mitochondrial fusion maintains TCR signaling and transcription factor activation such as NFAT, promoting the expression of effector molecules including IL-2. Mitochondria that are partially damaged can receive NADH, $FADH_2$ and TCA intermediates from healthy mitochondria through fusion, sustaining their ATP production capabilities. Mitochondrial fusion allows adjacent mitochondria to share mtDNA, metabolites and enzymes, maintaining OXPHOS activity, which is particularly important in the oxidative stress of TME. Moreover, MFN1 is involved in the clearance of damaged mitochondria through the ER-associated degradation pathway mediated by the polyubiquitination action of the E3 ubiquitin ligase Parkin (100).

Single-cell RNA sequencing analysis of $CD8^+$ T cells isolated from tumor samples has revealed that MFN2 expression levels gradually increase with $CD8^+$ T-cell activation and enhanced OXPHOS (101). $CD8^+$ T cells deficient in MFN2

exhibit decreased mitochondrial metabolism and function. MFN1/2, which drive outer membrane fusion, and OPA1, which drives inner membrane fusion, are key targets in controlling mitochondrial dynamics (2,102). MFN1/2 and OPA1 maintain mitochondrial OXPHOS function through fusion, providing energy support for $CD8^+$ T-cell survival and function, and sustaining intracellular signaling pathways, such as the mTOR pathway, which are crucial for $CD8^+$ T-cell activation and cytotoxicity (99). In tumor-bearing mice, drugs promoting mitochondrial fusion can extend the lifespan of effector $CD8^+$ T cells, and enhance their secretion of INF-γ and TNF-α (99). In addition, stimulating the T-cell surface receptor 4-1BB can enhance mitochondrial fusion and biogenesis in $CD8^+$ TILs (103).

Mitochondrial fission. Mitochondrial fission refers to the process where a mitochondrion divides to produce smaller and more dispersed mitochondria, assisting in the movement of mitochondria to regions requiring energy. Mitochondrial fission is primarily mediated by dynamin-related protein 1 (Drp1), which is recruited to the mitochondrial outer membrane, inducing mitochondrial constriction and fragmentation. Moderate fission benefits cell division and autophagy, but excessive fission can lead to mitochondrial fragmentation, loss of membrane potential, decreased ATP production and subsequently, cell apoptosis (104).

During T-cell activation, mitochondrial fission accelerators are required to facilitate mitochondrial division and upregulate calcineurin activity to activate Drp1 (105,106), inducing mitochondrial fission and inner membrane cristae remodeling, which ultimately leads to mitochondrial aggregation below the TCR clusters (43). An increase in mitochondrial numbers and inner membrane cristae remodeling aids in controlling glycolysis-associated signaling, serving an essential regulatory role in effector T-cell activation. T cells recognize antigens through forming an IS with APCs. During the activation process induced by TCR and CD28 co-stimulation, mitochondria rapidly produce and release ATP at the IS, increasing intracellular Ca^{2+} concentration, promoting T-cell activation and proliferation (107,108). T-cell activation requires mitochondrial translocation along the microtubule network to the IS, supporting sustained activation through maintenance of Ca^{2+} signals (109). At the IS, Drp1-mediated mitochondrial fission helps maintain intracellular Ca^{2+} levels, activating mTOR and cMyc signaling pathways, thereby promoting T-cell proliferation. Suppression of Drp1 expression hampers $CD8^+$ T-cell migration and effector functions (110). Mitochondrial fission, driven by GTPase Drp1 oligomerization, is vital for $CD8^+$ T-cell chemotaxis and infiltration, and controls mitochondrial distribution during cell proliferation. Changes in mitochondrial dynamics transform mitochondria from isolated 'energy factories' into functionally integrated metabolic communities, markedly enhancing the ability of the cell to adapt to environmental stress. This is particularly critical for maintaining T-cell function within the TME (70).

Mitochondrial transfer. Mitochondrial transfer is part of mitochondrial dynamics, involving various mechanisms such as gap junctions, nanotubes and extracellular vesicles (111). Tunnel nanotubes (TNTs) are one of the primary routes for mitochondrial transfer. Transport through nanotubes is a GTP-dependent process, with GTP primarily generated in the mitochondrial TCA cycle providing energy for mitochondrial dynamic changes and transport (112). Tumor cells can scavenge mitochondria from immune cells via nanotubes, causing unidirectional mitochondrial transfer from immune cells to tumor cells, enhancing mitochondrial respiration function, proliferation capacity and accelerating tumor progression (113). Tumor cells can transfer mitochondria to T cells through TNTs or extracellular vesicles, replacing existing mitochondria in T cells with mutated tumor cell mitochondria, thereby inhibiting the antitumor immune response of T cells (8). TNTs can effectively transfer mitochondria from bone marrow stromal cells to T cells, enhancing their metabolic abilities. When 'reengineered' T cells are transferred into tumor-bearing hosts, they exhibit vigorous proliferation, higher infiltration efficiency into tumors, reduced apoptosis rate and stronger antitumor capabilities (114).

5. mtDNA-mediated tumor immunity in T cells

Mitochondria and the nucleus maintain cellular homeostasis and mtDNA integrity through bidirectional signaling, coordinating stress responses, metabolic adaptation and cell survival (115,116). Anterograde signaling from the nucleus involves nuclear-encoded proteins such as TFAM, PGC-1α and NRF1/2 to regulate mitochondrial replication and repair in response to cellular needs (117,118). Conversely, mitochondria utilize retrograde signaling to relay metabolic stress signals such as changes in Ca^{2+}, ROS or NAD^+/NADH back to the nucleus, reprogramming gene expression to restore function (119,120). The integration of anterograde and retrograde signals constitutes mitonuclear communication, which is crucial for maintaining mtDNA integrity, particularly under stress conditions such as radiation. mtDNA is the genetic material within mitochondria, which has a key role in OXPHOS and energy metabolism in cells. Mutations in the mitochondrial genome are an important component of cancer mutant genomes (121). As a common intracellular damage-associated molecular pattern, mtDNA breakdown and release are crucial factors in mitochondrial dysfunction-mediated inflammation (122,123). Abnormal mitochondrial gene copy number, gene expression alterations and mtDNA epigenetic modifications often influence cancer occurrence and malignant transformation by regulating cellular metabolism, ROS production and intercellular interactions (124).

Excessive production of ROS causes oxidative stress, a major source of DNA damage (125). When cells experience oxidative stress, the integrity of the mitochondrial membrane is compromised, promoting the release of oxidized mtDNA into the cytoplasm, triggering IFN and pro-inflammatory responses (126,127). In the TME, the extracellular leakage of mtDNA is mainly mediated by extracellular vesicles composed of exosomes, microvesicles and apoptotic bodies. mtDNA can enter extracellular vesicles through direct contact or mitochondrial-derived vesicles, and then be transported into the extracellular space where it can be passively released during cell death through mechanical damage-mediated rupture of the cell membrane (128). Once released into the cytoplasm, mtDNA can be recognized by pattern-recognition receptors

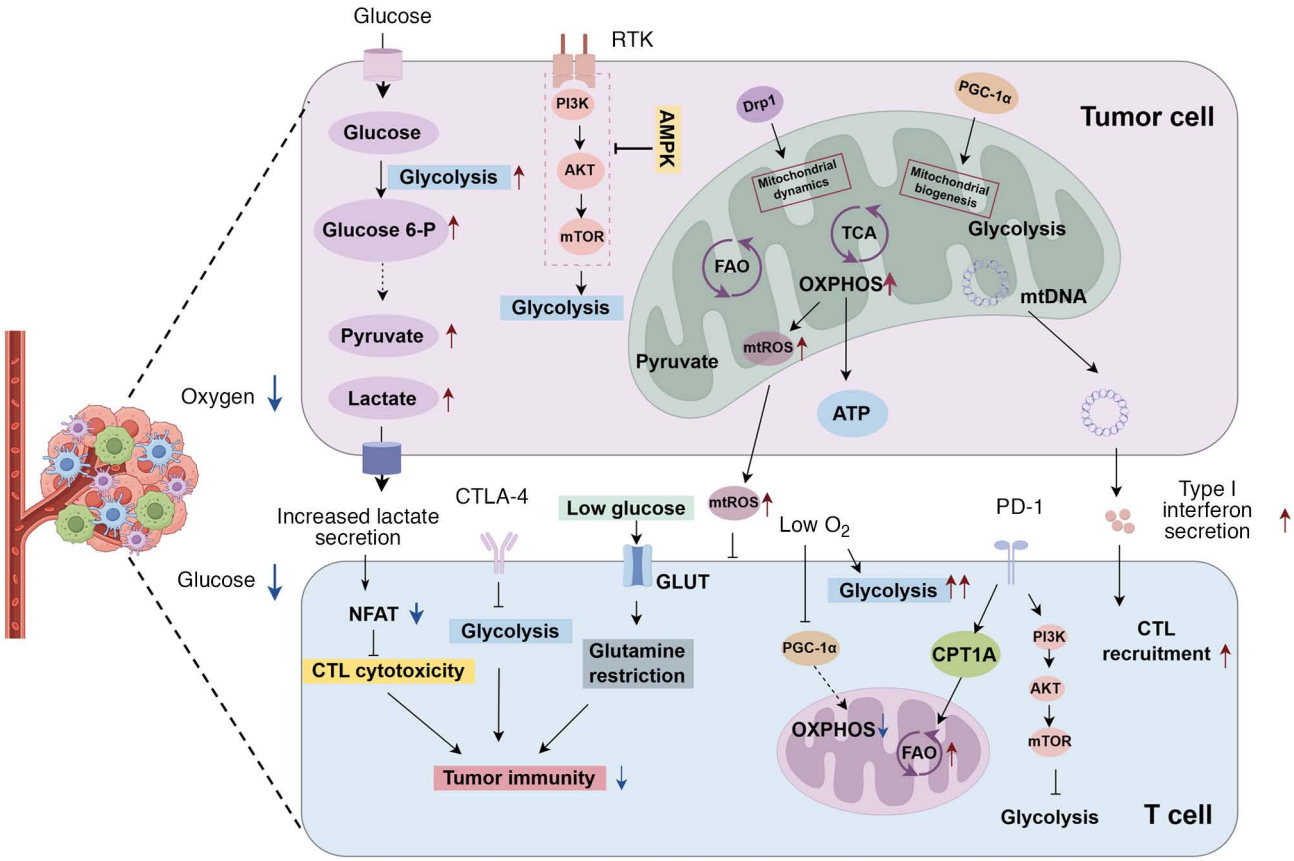

Figure 2. Mitochondria regulate T-cell tumor immunity pathways. Mitochondrial pathways that regulate T-cell tumor immunity tumor cells promote the production of a large number of mitochondrial ROS by upregulating aerobic glycolysis activity, mitochondrial division, mitochondrial biosynthesis and OXPHOS pathways, and high ROS levels promote the development of tumorigenesis by inhibiting tumor cell apoptosis, promoting tumor cell proliferation, epithelial-mesenchymal transformation, invasion and angiogenesis, and promoting the formation of an immunosuppressive microenvironment by inhibiting T-cell activation, promoting T-cell apoptosis and promoting immunosuppressive cell generation. Leakage of mtDNA into the cytoplasm and extracellular space promotes immune cell activation, promotes immunogenic cell death and enhances host antitumor immune activity by activating innate immune signals. mtDNA can also enter the extracellular space through extracellular vesicles, promoting immunosuppressive tumor microenvironment formation. Glutamine restriction refers to reducing the concentration of glutamine available to cells. CPT1A, carnitine palmitoyltransferase 1A; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Drp1, dynamin-related protein 1; FAO, fatty acid oxidation; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; OXPHOS, oxidative phosphorylation; PD-1, programmed death-1; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; ROS, reactive oxygen species; TCA, tricarboxylic acid.

such as cyclic GMP-AMP synthase (cGAS), Toll-like receptor (TLR)9, and NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3), activating downstream inflammatory signaling pathways, including the cGAS-stimulator of interferon genes (STING) pathway, TLR9-myeloid differentiation primary response 88-NF-κB pathway and NLRP3 inflammasome pathway. mtDNA stress elevates immunoproteasomes and MHC class I antigen presentation pathways through the cGAS/STING/type I IFN signaling pathway, leading to autonomous activation and proliferation of $CD8^+$ T cells (129).

Direct or indirect cell contact facilitates the transfer of mtDNA-mutated mitochondria from cancer cells to TILs, which exhibit metabolic abnormalities, cell senescence, functional defects, impaired memory formation and effector function (8). In melanoma models, mtDNA is kinetically released in an ATP-dependent manner into the cytosol, inducing PD-L1 expression through the STING-IFN pathway, promoting immune escape (130). mtDNA mutations render tumors more sensitive to immune checkpoint blockade (ICB) therapies; alterations in redox balance caused by mtDNA mutations increase tumor sensitivity to ICB (131). How mitochondria regulate T-cell tumor immunity pathways is illustrated in Fig. 2.

6. Targeted mitochondrial therapy for tumors

Mitochondrial dysfunction within the TME is a notable reason for the impaired antitumor immune response and antitumor activity in response to diverse immunotherapies. Targeting mitochondrial energy metabolism, mitochondrial dynamics and other mitochondrial physiological processes to rebuild T-cell antitumor function has proven effective in some cancer models (70,132,133). Therefore, regulating mitochondrial metabolism, dynamics or other physiological processes, and increasing mitochondrial quality to restore T-cell antitumor activity may be a new strategy for cancer treatment in the future.

Targeting mitochondrial metabolism to enhance T-cell antitumor immunity. The activity of enolase 1 in tumor-infiltrating $CD8^+$ T cells is impaired, limiting glycolytic processes and glucose metabolism, which can be restored by enhancing

enolase 1 activity or supplementing with exogenous phosphoenolpyruvate and pyruvate, thereby restoring glucose metabolism and antitumor activity in $CD8^+$ T cells (134). In aging tumor-bearing mice, the content of spermidine (SPD) in $CD8^+$ T cells is markedly reduced. SPD enhances FAO activity by binding the mitochondrial trifunctional protein complex, thus boosting $CD8^+$ T cell-mediated antitumor immunity (135). Tetrahydrobiopterin (BH4) is involved in regulating mitochondrial respiration and is essential for $CD8^+$ T-cell expansion; increasing BH4 or overexpressing BH4 synthase GTP cyclohydrolase 1 can enhance $CD8^+$ T-cell antitumor activity and inhibit tumor progression (136). An epigenetic activator EnPGC-1, developed based on DNA, can enhance mitochondrial activation, energy metabolism and $CD8^+$ T-cell proliferation *in vitro*, synergizing with PD-1 blockade to boost antitumor immunity, thereby improving host survival (137).

$CD8^+$ T cells overexpressing PGC-1α exhibit higher levels of OXPHOS and greater spare respiratory capacity, have longer survival times and possess stronger antitumor effects (66). Enhancing PGC-1α expression and activity restores T-cell mitochondrial function and metabolic reprogramming, leading to increased cytokine production and enhanced antitumor effects. ROS precursors or mitochondrial uncouplers produce ROS to synergistically enhance the antitumor effects of PD-1 blockade therapy through intratumoral effector/memory cytotoxic T lymphocytes (CTLs), increasing mTOR, AMPK and downstream transcription factors PGC-1α and T-box expressed in T cells expression; applying related activators can synergize with PD-1 blockade therapy (138). Targeted removal of extracellular ROS in tumors increases T-lymphocyte tumor infiltration, restoring T-cell antitumor immunity induced by immunogenic cell death (95).

Research on melanoma models has revealed that the use of PPARα agonists to promote FAO can enhance the ability of $CD8^+$ TILs to slow tumor progression (139). In addition, TILs with high expression of PGC-1α exhibit stronger mitochondrial adaptability and longer survival times within the tumor (66). These two pathways help recover energy and overcome exhaustion in tumor-infiltrating chimeric antigen receptor (CAR)-T cells. Mitochondrial dysfunction and HIF-1α-mediated glycolytic reprogramming contribute to T-cell exhaustion; using 2-deoxy-D-glucose pharmacological inhibitors to suppress glycolytic reprogramming is a viable metabolic intervention strategy to maintain CAR-T cell stemness, longevity and function during tumor immunotherapy (29). Targeting Regnase-1 enhances mitochondrial adaptability through basic leucine zipper ATF-like transcription factor, promoting effector T cells for tumor therapy and boosting tumor adoptive cell therapy (140). VDAC2, a protein located on the mitochondrial outer membrane, increases $CD8^+$ T-cell proportion in tumors lacking VDAC2, exhibiting stronger effector functions; targeting mitochondrial VDAC2 directly kills tumor cells and recruits more $CD8^+$ T cells to reshape the immune microenvironment (141).

Targeting mitochondrial dynamics to enhance T-cell antitumor immunity. Mitochondrial fusion is a key regulatory hub that determines the metabolic mode selection and functional vitality of T cells. In exhausted T cells, restricted mitochondrial fusion leads to abnormal mitochondrial morphology, impacting quality control and biosynthesis, inducing mitochondrial dysfunction and metabolic reprogramming (142). Targeting mitochondrial fusion to restore T-cell vitality and reverse exhaustion may become a novel strategy in tumor immunotherapy (143).

PGC-1α regulates mitochondrial function and quality by modulating fusion and fission processes. In the Lewis lung carcinoma mouse model, the PGC-1α agonist bezafibrate has been reported to markedly increase ROS in tumor-infiltrating effector CTLs and the expression of FAO-related genes in tumor tissues. This promoted an increase in C-X-C motif chemokine ligand (CXCL)9, CXCL10 and C-X-C motif chemokine receptor 3 receptor expression in infiltrating CTLs, supporting $CD8^+$ T-cell survival, infiltration and activation (144). Bezafibrate may further enhance CTL mitochondrial activation by upregulating OXPHOS and glycolysis, improving their proliferation and effector functions, increasing FAO rate and mitochondrial respiratory capacity to meet cellular energy demands, enhancing antitumor immunity (145).

The process by which tumor cells 'hijack' functional mitochondria from T cells via TNTs may constitute an alternative mechanism of immune evasion. Selectively inhibiting TNT formation could be considered a strategic approach to target mitochondrial involvement in antitumor activity. Current pan-inhibitors (such as farnesyltransferase inhibitors and cytochalasin) only partially suppress TNT formation due to a lack of specific markers (113,146). Studies have shown that mitochondrial transfer is highly related to actin filament regulators Pim-1 proto-oncogene, serine/threonine kinase, myosin IB, profilin-1, and Abl-interactor 1, which may serve as targets to disrupt TNTs (147,148). The cell adhesion molecule poliovirus receptor-related 2 (encoding Nectin-2) is also one of the top predictive markers for mitochondrial transfer (149). Additionally, mitochondrial transfer can improve $CD8^+$ T-cell mitochondrial quality and metabolic adaptability, proving useful in adoptive immunotherapy (114).

Tumor vaccines and mtDNA editing. Pierini *et al* (150) utilized abnormal mitochondrial proteins isolated from tumors to develop a cancer vaccine as an immunotherapeutic strategy. Sequencing of tumor mtDNA identified mutant proteins cyclooxygenase-1 (COX1) and mitochondrially encoded NADH dehydrogenase 5 (MT-ND5) for tumor mitochondrial vaccine production. COX1 mutant peptides, when utilized as vaccines, not only delayed tumor growth but also induced specific T-cell immune responses. Introducing a truncated mutation of mtDNA-encoded complex I gene MT-ND5 in mouse melanoma models has been reported to encourage Warburg-like metabolic shifts, remodeling the TME and persistently activating antitumor immune responses (131). Furthermore, mtDNA can strengthen antitumor immune effects in dendritic cell-derived extracellular vesicle vaccines for lung and pancreatic cancer (151).

Another direction in mitochondrial gene therapy is mtDNA genomic editing, a field where traditional tools such as CRISPR-Cas9 have excelled in nuclear DNA editing but face challenges, such as delivering Cas9 to mitochondria and off-target effects. The innovative transcription activator-like effector-linked deaminase (TALED) technology offers precise single-base conversion without DNA double-strand breaks,

enabling base editing. TALEDs facilitate adenine to guanine conversions, crucial for repairing mutations associated with mitochondrial diseases (152). An advanced study into TALED-induced mitochondria-driven precise base editing has elucidated reliance on the base excision repair pathway of cells, leading to enhanced TALEDs, which enable efficient mtDNA adenine base editing (153). Introducing or correcting mutations in cell and animal models allows more accurate exploration of the role of mtDNA in cancer metabolism (153). Future aims may include *in vitro* mtDNA editing to promote mitochondrial biogenesis and OXPHOS to address progressive mitochondrial quality loss in unmodified TILs.

Small molecule/nano-inducers targeting mitochondria. Abnormal mitochondrial function in tumor cells has positioned compound-based mitochondrial targeting as a promising strategy to eradicate chemoresistant cancer cells. Studies on small molecules/nano-inducers have focused primarily on mitophagy regulation and mitochondrial-targeted damage strategies (154,155). Development of mitochondrial nano-inducers targets selective mitophagy within autophagosomes to degrade mitochondria, markedly enhancing $CD8^+$ T-cell immune attacks by increasing MHC-I molecule expression, reducing the anti-apoptotic protein BCL-XL and releasing signaling molecules that activate T cells, thus improving antitumor immune responses (156). KCKT is an *in situ* transformable nanoparticle, and KCKT platform nanoparticles facilitate lysosomal escape and direct mitochondrial damage while blocking protective autophagy, notably enhancing drug delivery and mitochondrial targeting efficiency, providing a novel option for therapy (157). Azocarbonyl-propargyl-modified supramolecular albumin nanoparticles achieve targeted drug release in hypoxic tumor zones. For example, SHC4H nanoparticles co-release hydroxychloroquine and a mitochondrial-targeted photosensitizer to treat hypoxic tumors by modulating mitosis-induced oxidative stress cascades (158). TAEN is a developed modular acid/enzyme dual-gated nanotechnology platform, designed for efficient cascade drug delivery from lysosomes to mitochondria. TAEN uses hierarchical targeting to stabilize drug loading during circulation, selectively accumulate at tumor sites, and cascade-deliver drugs to mitochondria starting from lysosomes at the subcellular level. This nanotechnology effectively induces mtROS stress to cleave gasdermin-E, provoking tumor cell pyroptosis, enhancing tumor-killing efficiency by 30-50 times and activating antitumor immune responses (159).

7. Conclusions

Mitochondria are crucial organelles in tumor cell metabolic reprogramming. In addition to providing energy, they are critical in tumor cell survival, immune evasion, tumor progression and the immunosuppressive environment of hypoxic TMEs. Mitochondrial metabolic reprogramming provides energy and biosynthetic precursors, forming the basis for T-cell activation, proliferation and differentiation. Dynamic remodeling regulates the functional state of T cells, and maintaining mitochondrial quality is a key target to prevent T-cell exhaustion in the tumor TME and to enhance the effectiveness of immunotherapy. The present review discusses mitochondrial metabolism and biogenesis, dynamics, mtDNA interactions, mtROS involvement and the interplay with T cells in the TME, and antitumor immunity. The study aims to provide insights for developing innovative antitumor immunotherapies from the mitochondrial-tumor immunity perspective.

However, the discussion on mitochondrial targeted therapy in the present review lacks validation through large clinical cohorts, and prospective studies on mtDNA mutations and the efficacy of immunotherapy are still limited. More clinical research targeting mitochondria is needed in the future to facilitate the translation of theories into treatments. Additionally, although the study explores T-cell spatial heterogeneity, it lacks a systematic analysis of the patterns of mitochondrial defects and their immune impacts across different cancer types. Cross-cancer comparative studies are urgently needed to guide the development of precise immunotherapy strategies.

Current mitochondria-targeting immunotherapies incorporate mitochondrial-targeting drugs and immune checkpoint inhibitors to improve T-cell metabolic adaptability, reduce ROS damage and limit tumor energy supply, enhancing T-cell cytotoxicity. Targeting Drp1/MFN2 can restore T-cell mitochondrial morphology and function, reversing the exhausted state. Specific targeting and elimination of mutated DNA in the mitochondrial genome enables precise delivery of therapeutic genes. Small molecule/nano-inducers targeting mitochondria increase targeting precision and reduce off-target toxicity. However, mitochondrial targeting strategies, despite their theoretical promise, face multiple challenges in clinical translation. Firstly, there is a technical lack of efficient and specific mitochondrial targeting delivery systems. The dual-layer structure of the mitochondrial membrane and low lysosomal escape efficiency are major reasons for delivery failure (160,161). This requires a mechanistic analysis of the interaction between carriers and mitochondrial membranes, and the development of non-membrane potential-dependent targeting strategies. Secondly, viral vectors may induce immune responses, and the accumulation of nanomaterials in organs requires optimization through renal clearance engineering, with toxicity risks urgently needing evaluation (162,163). Lastly, regarding the demand for personalized treatment, mtDNA heterogeneity necessitates the development of patient-specific editing strategies, and clinical translation requires integration with patient-specific barrier profiles. With advancements in single-cell sequencing technology enhancing the resolution of mtDNA heterogeneity analysis, combined with artificial intelligence-driven predictive models, the future of mitochondrial medicine will focus on transforming mitochondrial disease treatment models from 'one-way intervention' to 'dynamic precision regulation', accelerating the clinical implementation of precision treatment technologies.

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Authors' contributions

MZ, ZL, YH and YY wrote the original draft. YX and KC restructured the manuscript's organization, edited the manuscript and created the figures. ZZ and DC reviewed and edited the manuscript. CZ acquired funding reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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