Mitochondrial dysfunction in T-cell exhaustion: Its contribution to the efficacy of cancer immunotherapy (Review)

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Abstract. Mitochondria play a pivotal role in the regulation of T-cell function, particularly in the context of T-cell exhaustion within the tumor microenvironment. T-cell exhaustion, characterized by impaired effector functions and the sustained expression of inhibitory receptors, poses a significant barrier to effective antitumor immunity and limits the success of immunotherapies. Emerging evidence indicates that mitochondrial dysfunction is a contributor to the metabolic and functional decline of tumor-infiltrating lymphocytes. The present review critically synthesizes the available mechanistic and translational literature on mitochondrial dysfunction in T-cell exhaustion, with particular attention paid to mitochondrial dynamics, mitophagy, and the threshold-dependent duality of mitochondrial reactive oxygen species. The evidence is organized not by pathway alone, but by intervention class and level of evidence, so that the strategies with demonstrated clinical traction can be distinguished from those that remain at the proof-of-concept stage. Of note, four intervention classes are discussed: Metabolic reprogramming, enhancement of mitochondrial biogenesis, redox-directed modulation and intercellular mitochondrial transfer, together with mitochondria-directed pharmacological and nanoscale delivery platforms. Clinical translation is assessed against trials registered on ClinicalTrials.gov, of which the most advanced evaluate metformin in combination with immune checkpoint inhibitors. Mitochondrial dysfunction is also placed in the context of other established drivers of exhaustion, the limitations of the available evidence are stated, and the specific questions that need to be answered before mitochondrial targeting can be incorporated into immunotherapy regimens are also stated. Rather than claiming that mitochondrial dysfunction is a single dominant constraint, it is argued herein that its therapeutic value lies in being a mechanistically tractable and pharmacologically accessible component of a multifactorial resistance program.

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Abbreviations: AMPK, AMP-activated protein kinase; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; DAMPs, damage-associated molecular patterns; DRP1, dynamin-related protein 1; ICB, immune checkpoint blockade; ICD, immunogenic cell death; ICIs, immune checkpoint inhibitors; MFN1/2, mitofusin 1/2; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; mtROS, mitochondrial reactive oxygen species; NRF1/2, nuclear respiratory factor 1/2; Nrf2, nuclear factor erythroid 2-related factor 2; OPA1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PINK1, PTEN-induced kinase 1; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; Sirt3, sirtuin 3; Sod2, superoxide dismutase 2; TFAM, mitochondrial transcription factor A; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment; TPP, triphenylphosphonium; Tregs, regulatory T-cells; USP30, ubiquitin-specific protease 30

Key words: mitochondria, T-cell exhaustion, tumor immunotherapy, mitochondrial dynamics

Contents

1. Introduction
2. Association between mitochondrial function and T-cell exhaustion
3. Strategies targeting mitochondria
4. Redox-directed interventions: Antioxidants and reactive oxygen species
5. Mitochondrial transfer and mitochondria-directed agents

6. Combination with immune checkpoint inhibitors: Evidence and clinical translation
7. Summary and future directions
8. Conclusion

1. Introduction

T-cells are pivotal players in the defense of the immune system against tumors, orchestrating targeted immune responses that can lead to the elimination of cancer cells. Their central role in antitumor immunity has been substantiated by the success of various immunotherapeutic approaches, notably immune checkpoint blockade (ICB) therapies, which aim to reinvigorate exhausted T-cells within the tumor microenvironment (TME) (1,2). However, despite these advances, the efficacy of immunotherapy remains limited in many cancer types. The principal reason is T-cell exhaustion, a state of hypofunction characterized by impaired proliferative capacity, reduced cytokine production and sustained expression of inhibitory receptors, such as programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing 3 and T-cell immunoreceptor with immunoglobulin and ITIM domains (3,4). Exhausted T-cells exhibit a spectrum of differentiation states, ranging from progenitor or stem-like exhausted T-cells that retain proliferative potential to terminally exhausted cells with severely diminished effector functions (1,5). This exhaustion is often driven by chronic antigen stimulation in the immunosuppressive milieu of the TME, which includes factors such as hypoxia, regulatory T-cells (Tregs), metabolic stress and immunosuppressive cytokines (3,4). Importantly, exhausted T-cells not only lose their antitumor efficacy but may also acquire immunosuppressive functions, further dampening the immune response (4). Understanding the molecular and cellular underpinnings of T-cell exhaustion is therefore crucial for developing strategies to restore T-cell functionality and improve cancer immunotherapy outcomes.

A growing body of evidence implicates mitochondrial dysfunction as one of several contributors to T-cell exhaustion and impaired antitumor immunity. Mitochondria are essential organelles that regulate cellular metabolism, bioenergetics, reactive oxygen species (ROS) generation, calcium signaling and apoptosis, all critical processes for T-cell activation, differentiation and effector function (6,7). Within the TME, T-cells frequently encounter metabolic challenges, such as nutrient deprivation, hypoxia and increased oxidative stress, which compromise mitochondrial integrity and function (8,9). These mitochondrial perturbations manifest as reduced oxidative phosphorylation (OXPHOS) capacity, mitochondrial depolarization, increased ROS production, and defective mitochondrial dynamics, including impaired mitophagy and altered fission/fusion balance (10). Such dysfunction leads to bioenergetic insufficiency and metabolic reprogramming that favor T-cell exhaustion, characterized by epigenetic and transcriptional changes that lock T-cells into hypofunctional states (11). For instance, accumulation of depolarized mitochondria in tumor-infiltrating lymphocytes (TILs) is linked to terminal exhaustion and diminished responsiveness to ICB. Moreover, mitochondrial metabolic intermediates and signaling pathways, including those involving pyruvate metabolism, have been shown to influence T-cell fate decisions and effector functions (12). Collectively, these findings underscore the critical role of mitochondrial health in sustaining effective antitumor T-cell responses and highlight mitochondrial dysfunction as a key mechanism driving T-cell exhaustion in cancer.

Given the integral role of mitochondrial dysfunction in T-cell exhaustion, restoring mitochondrial fitness presents a promising therapeutic avenue to rejuvenate exhausted T-cells and enhance their antitumor efficacy. Recent research has explored various strategies targeting mitochondrial metabolism to reverse exhaustion and improve immunotherapy responses. These include the pharmacological induction of mitochondrial biogenesis via peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) activation, antioxidant therapies to mitigate ROS-induced damage, the modulation of mitochondrial dynamics to promote mitophagy and quality control, and metabolic reprogramming to enhance OXPHOS and ATP production (11). Innovative approaches, such as mitochondrial transplantation have emerged, whereby functional mitochondria are transferred into exhausted T-cells, resulting in enhanced mitochondrial respiration, increased proliferation, reduced exhaustion markers and improved tumor control in preclinical models (13,14). Additionally, targeting signaling pathways that regulate mitochondrial metabolism, such as MEK inhibition to reduce bioenergetic demand or modulation of lipid metabolism to restore mitochondrial activity, has shown potential in alleviating T-cell exhaustion (15,16). Combining mitochondrial-targeted therapies with existing immunotherapies, including immune checkpoint inhibitors (ICIs) and adoptive T-cell transfer, has demonstrated synergistic effects in overcoming T-cell dysfunction and promoting durable antitumor immunity (17,18). These advances highlight the therapeutic promise of mitochondria-focused interventions to reinvigorate exhausted T-cells and augment cancer immunotherapy efficacy.

Several reviews have examined mitochondrial metabolism in T-cells, and the mechanistic ground covered in the present review overlaps with theirs (6,11,19). Of note, three features distinguish the present review from those syntheses. First, it is organized around intervention class and level of evidence rather than around pathways: For each candidate strategy, what has been demonstrated is stated, in which model system, and how far it has progressed towards clinical practice, in order for the reader to be able to see which approaches merit clinical evaluation and which remain exploratory. Second, it treats mitochondrial dysfunction explicitly as one of several determinants of immunotherapeutic resistance rather than as a single dominant constraint, and compares it directly with the other recognized drivers of exhaustion. Third, it incorporates registered clinical trials rather than preclinical findings alone; thus, the gap between mechanism and clinical translation is visible rather than implied. Where the evidence is contradictory, this is stated and an explanation is proposed, rather than presenting the field as settled.

The present review is a critical review rather than a systematic review, and no quantitative synthesis was attempted. To ensure that the literature base is nevertheless transparent, the authors searched the PubMed, Web of Science and Scopus

databases for publications indexed up to September 27, 2026. Search terms were combined from the following list: Mitochondria, mitochondrial dysfunction, mitochondrial dynamics, mitophagy, oxidative phosphorylation, reactive oxygen species, T-cell exhaustion, TILs and ICI. Reference lists of the retrieved articles were screened for additional sources, and ClinicalTrials.gov was searched on September 27, 2026 for registered trials of mitochondrial and metabolic agents combined with ICIs. Priority was given to primary studies published from 2019 onwards and to reviews that have shaped the current consensus. Studies were included if they reported a mechanistic or therapeutic link between mitochondrial function and T-cell exhaustion in cancer. Studies were excluded if mitochondrial read-outs were not reported, or if the report was purely descriptive. As the included evidence is predominantly preclinical and heterogeneous in model system, intervention dose and timing, and endpoint definition, findings are reported qualitatively and graded by level of evidence rather than pooled.

2. Association between mitochondrial function and T-cell exhaustion

Role of mitochondria in T-cell energy metabolism. Mitochondria are central to T-cell energy metabolism, primarily through their role in OXPHOS, which efficiently generates ATP to meet the high bioenergetic demands of T-cells during activation, proliferation and effector functions. Upon antigen stimulation, naïve T-cells undergo metabolic reprogramming that involves a shift from a quiescent state to a highly active metabolic state characterized by increased mitochondrial biogenesis and OXPHOS to support clonal expansion and effector differentiation. This mitochondrial energy production is indispensable for $CD8^+$ T-cells, which rely on mitochondrial metabolism not only for ATP generation, but also for sustaining their migration, effector differentiation and cytotoxic activity within the tumor microenvironment (19,20). Furthermore, mitochondrial metabolic flexibility, including the ability to utilize different substrates, such as pyruvate and fatty acids, is critical for maintaining $CD8^+$ T-cell antitumor immunity. The disruption of key mitochondrial enzymes, such as protein tyrosine phosphatase mitochondrial 1, impairs mitochondrial substrate utilization, leading to oxidative stress, DNA damage, and apoptosis, which collectively diminish T-cell function and promote tumor progression (21). The metabolic reprogramming in T-cells involves coordinated regulation of mitochondrial dynamics, biogenesis and quality control mechanisms, which ensure mitochondrial fitness necessary for sustained immune responses (8,11). Additionally, mitochondrial metabolism intersects with signaling pathways, such as mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), which regulate T-cell differentiation and memory formation by modulating mitochondrial function and energy production (22,23). Mitochondria also generate ROS and regulate calcium signaling, which influence T-cell activation and survival; however, excessive mitochondrial ROS or dysfunctional calcium flux can lead to T-cell exhaustion or apoptosis (24,25). Notably, mitochondrial dysfunction in T-cells, characterized by depolarization, reduced respiratory capacity and impaired mitophagy, is associated with diminished antitumor efficacy and T-cell exhaustion in chronic infections and cancer (26). Therapeutic strategies aimed at enhancing mitochondrial function, such as promoting mitochondrial biogenesis, improving substrate flexibility, or modulating mitochondrial dynamics, have shown promise in restoring T-cell metabolic fitness and antitumor immunity (11,27). In summary, mitochondria serve as the powerhouse of T-cells by providing ATP through OXPHOS and integrating metabolic and signaling pathways essential for T-cell activation, differentiation, and effector functions. Metabolic remodeling of mitochondria is thus a pivotal determinant of T-cell fate and function, with significant implications for immunotherapy and cancer treatment (Table I).

Mechanisms of mitochondrial dysfunction. Mitochondrial dysfunction in T-cells is a multifaceted process that critically impairs their antitumor efficacy, with oxidative stress and metabolic byproducts playing central roles. One pivotal mechanism involves mitochondrial oxidative stress, primarily mediated by the overproduction of ROS. Excessive mitochondrial ROS (mtROS) disrupts mitochondrial membrane potential and damages mitochondrial DNA (mtDNA), leading to impaired OXPHOS and ATP synthesis. This oxidative damage triggers mitochondrial swelling, depolarization and the activation of apoptotic pathways, culminating in T-cell exhaustion or death. For example, in autoimmune conditions, elevated mitochondrial oxidative stress in Tregs is associated with DNA damage response activation and cell death, underscoring the detrimental impact of ROS on T-cell viability and function (28). Similarly, in effector $CD8^+$ T-cells, mitochondrial oxidative stress induced by metabolic stressors or environmental insults, such as ammonia accumulation leads to mitochondrial and lysosomal damage, impairing autophagic flux and promoting cell death (29,30). The accumulation of mitochondrial damage-associated molecular patterns (DAMPs), such as mtDNA in the cytosol, can further activate innate immune pathways, such as the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, influencing T-cell function and antitumor immunity (31,32). Thus, mitochondrial oxidative stress represents a critical node linking mitochondrial damage to T-cell dysfunction.

Beyond oxidative stress, metabolic byproducts, such as lactate and fatty acids exert suppressive effects on T-cells by modulating mitochondrial function. TMEs often harbor elevated levels of lactate due to the Warburg effect, which impairs T-cell metabolism and effector function. Lactate accumulation leads to intracellular acidification and inhibits mitochondrial respiration, thereby reducing ATP production and cytokine secretion by T-cells (33). Moreover, fatty acids, particularly unsaturated fatty acids such as linoleic acid, can induce mitochondrial dysfunction in T-cells by promoting mitochondrial reactive oxygen species generation and lipid peroxidation, resulting in mitochondrial depolarization and apoptosis (34). Other fatty acids act in the opposite direction: Oleic acid restores the antitumor immunity of γδ-T-cells that is impaired by palmitic acid (35). The uptake and mitochondrial transport of fatty acids are facilitated by proteins, such as epidermal fatty acid-binding protein, which mediates the incorporation of fatty acids into mitochondrial membranes, exacerbating mitochondrial stress and impairing antitumor

Table I. Role of mitochondria in T-cell function and metabolism.

Aspect	Mechanism	Model system	Level of evidence	(Refs.)
Central role in energy metabolism	Mitochondria generate ATP by OXPHOS to meet the bioenergetic demand of activation, proliferation and effector function	Human and murine T-cells	Mechanistic	(6,7)
$CD8^+$ T-cell dependence	Mitochondrial metabolism sustains migration, polarization and cytotoxic activity within the tumor	Murine and human $CD8^+$ T-cells	Mechanistic	(19,20)
Metabolic flexibility and enzyme disruption	Disruption of PTPMT1 impairs substrate utilization, causing oxidative stress, DNA damage and apoptosis	Murine $CD8^+$ T-cells	Mechanistic	(21)
Mitochondrial dynamics in reprogramming	Coordination of dynamics, biogenesis and quality control maintains mitochondrial fitness for sustained responses	Murine and human T-cells	Mechanistic	(8,11)
Signaling pathway intersection	mTOR and AMPK integrate environmental cues to regulate T-cell differentiation and memory formation	Murine T-cells	Mechanistic	(22,23)
ROS and calcium signaling	Mitochondrial ROS and calcium flux influence activation and survival; excess drives exhaustion or apoptosis	Murine and human T-cells	Mechanistic	(24,25)
Mitochondrial dysfunction	Depolarization, reduced respiratory capacity and impaired mitophagy associate with diminished antitumor efficacy	Human T cells (chronic lymphocytic leukemia)	Translational	(26)
Therapeutic strategies	Enhancing biogenesis, substrate flexibility or dynamics restores metabolic fitness and antitumor immunity	Murine tumor models	Animal	(11,27)

The levels of evidence follow the definitions provided below in the footnote to Table IV. OXPHOS, oxidative phosphorylation; PTPMT1, protein tyrosine phosphatase mitochondrial 1; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase.

T-cell responses. Additionally, aging-associated ceramide accumulation within mitochondria inhibits key signaling pathways, such as protein kinase A, promoting mitophagy and mitochondrial dysfunction that attenuate T-cell antitumor activity (36). These metabolic byproducts thus create a hostile metabolic milieu that compromises mitochondrial integrity and T-cell function.

Among the most well-characterized mechanisms is the disruption of mitochondrial dynamics, the continuous balance between fusion and fission that determines mitochondrial morphology, distribution and quality. Fusion of the outer mitochondrial membrane is mediated by mitofusin (MFN)1 and MFN2, whereas inner membrane fusion requires optic atrophy 1 (OPA1); fission is driven principally by dynamin-related protein 1 (DRP1), which is recruited to the outer membrane to constrict and divide the organelle. In healthy T-cells, these proteins are not interchangeable. Effector T-cells favor a punctate, fission-prone network that supports aerobic glycolysis and migration to the tumor site. Memory T-cells, by contrast, adopt an elongated, fused network that sustains OXPHOS and fatty acid oxidation. OPA1 is required for the expansion and metabolic fitness of effector $CD8^+$ T-cells (37). In TILs, however, this program becomes maladaptive. $CD8^+$ TILs accumulate mitochondria with altered cristae and reduced respiratory capacity, exhibit excessive DRP1-dependent fission, and display a fragmented network that reinforces exhaustion, such that restoring fusion improves their persistence (8). Conversely, DRP1 activity is required for the formation of memory $CD8^+$ T-cells and for their secondary responses, so that complete suppression of fission is not beneficial (38). A further layer of complexity is that tumor cells exploit the same machinery in the opposite direction: OPA1-dependent fusion in tumor epithelium supports respiratory function and reduces sensitivity to $CD8^+$ T-cell killing (39). The therapeutic implication is that mitochondrial dynamics should be modulated in a cell-type-, time- and context-dependent manner rather than pushed uniformly in one direction. Mitochondrial morphology is therefore best regarded as a tunable variable rather than as a defect to be corrected. How this plasticity should be exploited in the clinic, and whether the fusion-fission balance in human TILs is reversible under checkpoint blockade remains unresolved.

Mitophagy and mitochondrial quality control. Mitochondrial morphology is only one arm of quality control; the selective autophagic removal of damaged organelles, or mitophagy, is the other, and it is directly implicated in exhaustion. In exhausted CD8$^+$ T-cells, mitophagic flux is suppressed, and the resulting accumulation of depolarized, ROS-emitting mitochondria sustains the metabolic stress that locks T-cells into a hypofunctional state (40). The canonical pathway is initiated when PTEN-induced kinase 1 (PINK1) accumulates on the outer membrane of damaged mitochondria and recruits the E3 ubiquitin ligase Parkin, which ubiquitylates outer membrane proteins and targets the organelle for autophagic degradation. This process is opposed by the deubiquitinase ubiquitin-specific protease 30 (USP30), which removes Parkin-generated ubiquitin chains. USP30 is induced downstream of T-cell receptor and NFATc1 signaling in repeatedly stimulated T-cells, and its deletion or pharmacological inhibition restores mitophagy, improves mitochondrial fitness, rejuvenates effector function, and enhances antitumor immunity in preclinical models (40).

Mitophagy is not merely a housekeeping function; it is a determinant of T-cell fate. Urolithin A, a gut-microbiome-derived metabolite of ellagitannins, drives PINK1-dependent mitophagy in CD8$^+$ T-cells and promotes the expansion of T-memory stem cells with superior antitumor activity. The effect is mediated by release of the mitochondrial phosphatase PGAM5, which dephosphorylates beta-catenin and drives Wnt signaling together with compensatory mitochondrial biogenesis (41). These findings indicate that enhancing mitophagy and enhancing biogenesis are not competing options but complementary parts of a single quality-control axis, and that this axis is pharmacologically accessible with compounds already in clinical development for other indications. Whether mitophagy can be modulated selectively in T-cells without increasing it in tumor cells, where the same pathway limits cGAS-STING-dependent immunogenicity, remains an open and critical question.

Overall, the mechanisms reviewed in this section are not competing explanations, but rather convergent contributors to a single phenotype, and the supporting evidence for each differs in strength. The contribution of mitochondrial oxidative damage to T-cell dysfunction is consistent across independent murine and human systems and can be regarded as established at the animal level (28-32); the causal links between the individual dynamin-family GTPases and exhaustion in human TILs rest mainly on murine genetic studies and remain to be confirmed in human cells (8,37-39). Where findings conflict, the conflict concerns the direction of the required intervention rather than the existence of the phenotype: A fragmented, fission-prone network accompanies exhaustion, yet fission is also required for memory formation and recall responses, so that suppressing it entirely is not beneficial (8,38); and the same proteins serve the opposite purpose in tumor cells, where OPA1-dependent fusion lowers their sensitivity to CD8$^+$ T-cell killing (39). The comparative assessment made herein is that the mechanisms differ in how well they are supported. Oxidative damage is the most well supported, being documented in both murine and human systems; mitophagy occupies an intermediate position, since it is documented in murine models and can be manipulated pharmacologically with agents already in clinical development; and the individual dynamin-family proteins are the least well supported, as the human evidence is largely correlative. Across all of these, the read-out most consistently associated with exhaustion, and the one we recommend be reported routinely, is the combination of reduced spare respiratory capacity with accumulation of depolarized mitochondria. These mechanisms provide the foundation for the intervention classes discussed below (Table II) (25,29-34,36,42).

3. Strategies targeting mitochondria

Metabolic reprogramming. Metabolic reprogramming is a pivotal mechanism by which T-cells restore and sustain their energy supply, thereby enhancing their antitumor functions. Upon activation, T-cells undergo profound metabolic shifts to meet increased bioenergetic and biosynthetic demands essential for proliferation, differentiation, and effector activities. This metabolic remodeling primarily involves a transition from OXPHOS in naïve T-cells to enhanced glycolysis and mitochondrial oxidative metabolism in activated T-cells, facilitating rapid ATP generation and biosynthesis of macromolecules. Mitochondria serve as critical regulators in this process, orchestrating metabolic plasticity and signaling pathways that underpin T-cell immunity. For instance, CD28 co-stimulation has been shown to reinvigorate tumor-infiltrating CD8$^+$ T-cells by augmenting glycolysis and mitochondrial oxidative metabolism, which restores mitochondrial mass, membrane potential and fusion dynamics, directly correlating with enhanced T-cell activation and effector function (43). Conversely, mitochondrial dysfunction, characterized by depolarization and impaired mitophagy, contributes to T-cell exhaustion within the TME, underscoring the importance of maintaining mitochondrial fitness for effective antitumor immunity. Therapeutic interventions targeting mitochondrial metabolism, such as supplementation with nicotinamide riboside, have demonstrated the capacity to enhance mitochondrial fitness and responsiveness to ICB, highlighting metabolic reprogramming as a promising strategy to reverse T-cell exhaustion. Furthermore, metabolic reprogramming is not limited to glucose metabolism; fatty acid oxidation and amino acid metabolism also play integral roles. For example, stimulation with superantigen mutants can upregulate fatty acid uptake and mitochondrial energy metabolism in CD8$^+$ T-cells via the mTOR/peroxisome proliferator-activated receptor (PPAR)γ/SREBP1 and p38-MAPK signaling pathways, which are essential for T-cell activation and effector functions (44). Targeting these metabolic pathways can modulate T-cell fate and function, as demonstrated by genetic ablation of ATPase inhibitory factor 1 (IF1), which impairs glycolysis, mitochondrial biogenesis and the proliferation of T-lymphocytes, thereby compromising immune responses (45). Beyond intrinsic metabolic regulation, the tumor microenvironment imposes metabolic constraints such as nutrient deprivation and hypoxia, which disrupt T-cell metabolism and function. Hypoxia, for instance, profoundly remodels the T-cell surface proteome and metabolic state, leading to immunosuppression (46). Strategies that alleviate these metabolic stresses, including pharmacological agents such as metformin, have been shown to reprogram tryptophan metabolism in colorectal cancer, restoring amino acid availability and enhancing CD8$^+$ T-cell cytotoxicity (47). Additionally, the modulation

Table II. Mechanisms of mitochondrial dysfunction in T-cells.

Factor	Mechanism of action	Effect on T-cells	Model system	Level of evidence	(Refs.)
ROS	Damages mitochondrial and lysosomal membranes; impairs autophagic flux	Promotes cell death and disrupts T cell function	Murine and human T-cells	Mechanistic	(29,30)
Mitochondrial DNA (mtDNA)	Accumulates in the cytosol; activates the cGAS-STING innate immune pathway	Influences T-cell function and antitumor immunity	Murine T-cells	Mechanistic	(31,32)
Lactate	Causes intracellular acidification; blocks NFAT upregulation and inhibits mitochondrial respiration	Reduces ATP production and cytokine secretion; impairs effector function	Murine melanoma; human melanoma correlates	Animal/ translational	(33)
Fatty acids (linoleic acid)	Promotes mitochondrial ROS generation and lipid peroxidation	Induces mitochondrial depolarization and apoptosis	Murine mammary tumor models; $CD8^+$ T-cells	Animal	(34)
E-FABP (FABP5)	Chaperones fatty acid trafficking and mitochondrial transport; promotes linoleic acid incorporation into cardiolipin in the mitochondrial membrane	Exacerbates mitochondrial stress and impairs antitumor responses	Murine $CD8^+$ T-cells (adoptive transfer)	Animal	(34)
Ceramide	Accumulates in mitochondria; inhibits protein kinase A signaling	Promotes mitophagy and mitochondrial dysfunction; attenuates antitumor activity	Murine T-cells	Mechanistic	(36)
Fission, fusion and mitophagy	Disrupted by oxidative stress and metabolic byproducts, leading to imbalanced quality control	Accumulation of dysfunctional mitochondria; exacerbates metabolic stress	Murine and human T-cells (review)	Mechanistic	(42)
Calcium dysregulation	Secondary to oxidative damage; disrupts mitochondrial metabolism	Triggers apoptosis and depletes functional T-cells	Murine and human T-cells (autoimmune model)	Mechanistic	(25)

The levels of evidence follow the definitions provided in the footnote to Table IV. cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; ROS, reactive oxygen species.

of mitochondrial biogenesis and dynamics through pathways involving PGC-1α can boost T-cell metabolic capacity and antitumor efficacy (48). Collectively, these findings emphasize that metabolic reprogramming, through the enhancement of glycolysis, mitochondrial function and amino acid metabolism, constitutes a fundamental approach to restore and potentiate T-cell energy supply and antitumor activity (Fig. 1). Therapeutic strategies that target these metabolic pathways hold significant promise for overcoming T-cell dysfunction in cancer and improving immunotherapeutic outcomes (19,49,50).

Taken together, the routes discussed in this subsection are of unequal strength. The clearest element is that the metabolic state of activated and tumor-infiltrating $CD8^+$ T-cells can be shifted toward oxidative metabolism by co-stimulatory signaling, which restores mitochondrial mass and membrane potential and is associated with improved effector function in murine tumor models and human T-cells (43). The evidence for the remaining routes is far more fragmented: Substrate handling and fatty-acid trafficking (44), the ATP synthase inhibitory protein IF1 (45) and tryptophan metabolism under metformin (47) are each drawn from a single model system, no two of them have been compared in the same model, and the interventions concerned also act on other cells of the tumor microenvironment, so that the observed benefit cannot be attributed to T-cells alone (48,50). A further difficulty is that where the node under study lies downstream of the T-cell receptor, the direction in which it should be pushed is not self-evident, because hypoxia remodels the effector program rather than removing a single limiting substrate (46). The restoration of mitochondrial content and oxidative metabolism

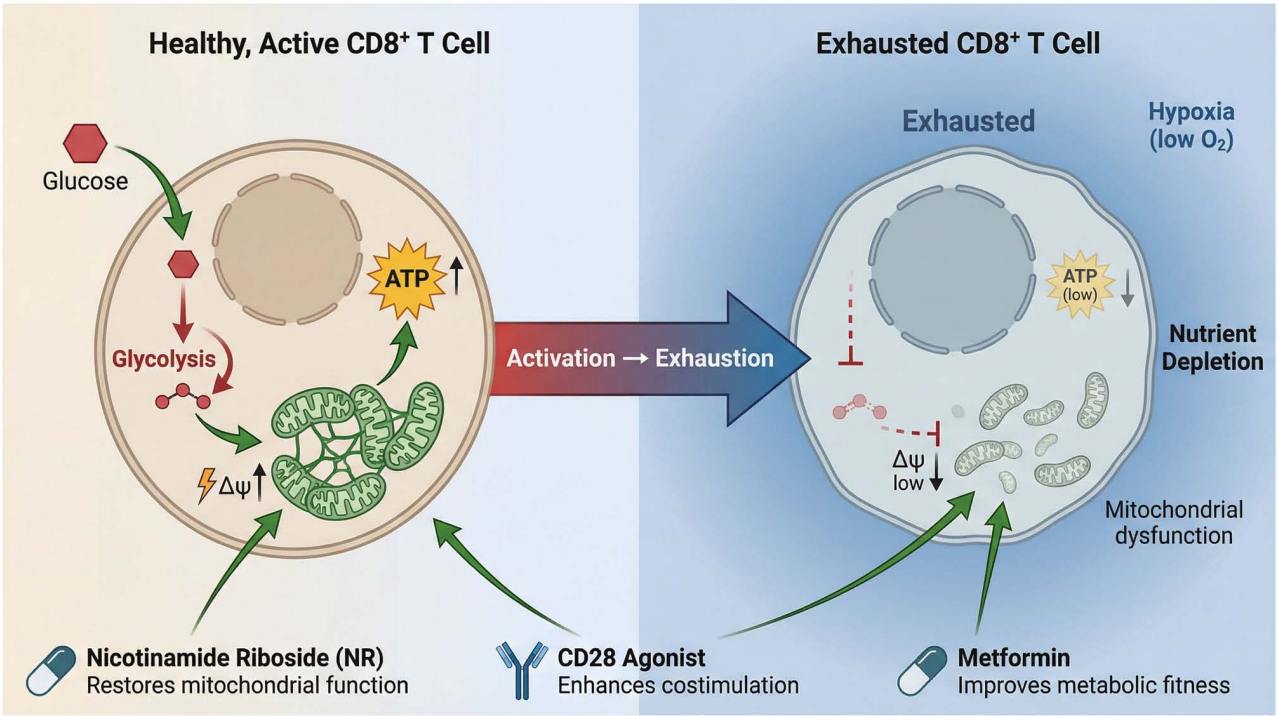


Figure 1. T cell metabolic reprogramming and its interaction with the tumor microenvironment. An active CD8+ T cell (left panel) is contrasted with an exhausted CD8+ T cell within the tumor microenvironment (right panel). The active cell takes up glucose, sustaining glycolysis and a fused, elongated mitochondrial network with a high mitochondrial membrane potential (Δψ) and efficient ATP production. Chronic antigen exposure within the tumor microenvironment, together with hypoxia and nutrient depletion, is accompanied by a fragmented mitochondrial network, the loss of membrane potential and reduced ATP generation and by the exhausted phenotype. Three interventions acting on this axis are shown: Nicotinamide riboside, CD28 agonists and metformin. The key mechanism is the following: The transition from the active to the exhausted state is a coordinated loss of glycolytic input and of mitochondrial respiratory capacity rather than a single lesion. Mitochondrial morphology is set by fusion, which requires optic atrophy 1, and by dynamin-related protein 1-dependent fission, and is coupled to mitochondrial quality control; sustained mitochondrial reactive oxygen species damage the inner membrane and mitochondrial DNA, impairing OXPHOS and ATP synthesis. Direction of effect. Loss of mitochondrial function is shown as inhibitory to effector function. Nicotinamide riboside, CD28 agonists and metformin are each shown as positively regulating mitochondrial mass, membrane potential and oxidative metabolism. Therapeutic implication. Mitochondrial capacity is a modifiable determinant of the exhausted phenotype and is therefore a plausible target for restoring responsiveness to immunotherapy; the three interventions shown are at different stages of clinical evaluation. Evidence basis. The metabolic and dynamic changes shown derive from mechanistic and animal studies in murine and human CD8+ T cells (8,28-32,37-39). The CD28 data are from murine tumor models and human T-cells (43). The clinical evaluation of metformin combined with checkpoint blockade is summarized in Table III, including a phase 1 study in which a mitochondrial endpoint was pre-specified (NCT03311308).

is therefore regarded as the element of this subsection most ready for clinical exploration, and the pharmacological modulation of individual metabolic enzymes as exploratory (Fig. 1).

Enhancing mitochondrial biogenesis. Mitochondrial biogenesis is a fundamental cellular process that increases mitochondrial mass and function, thereby enhancing cellular energy capacity and metabolic fitness. In T-cells, particularly CD8+ subsets, mitochondrial biogenesis is crucial for sustaining activation, proliferation, and antitumor functions. The activation of mitochondrial biogenesis pathways improves mitochondrial quality, promotes OXPHOS, and supports the energetic demands of effector and memory T-cells. One of the central regulators of mitochondrial biogenesis is PGC-1α. It orchestrates the transcription of nuclear and mitochondrial genes involved in mitochondrial replication and function, including nuclear respiratory factors (NRF1/2) and mitochondrial transcription factor A (TFAM). Pharmacological or genetic interventions targeting these pathways have demonstrated the ability to enhance mitochondrial biogenesis, thereby improving T-cell metabolic fitness and antitumor efficacy.

Several studies have provided compelling evidence that activating mitochondrial biogenesis pathways can restore or augment T-cell function in cancer settings. For example, enforced expression of PGC-1α in CD8+ T-cells promotes mitochondrial biogenesis, enhances oxidative metabolism, and improves memory formation, leading to superior antitumor immunity in murine melanoma models (51). Similarly, the targeted epigenetic activation of PGC-1α/β using DNA-based activators enhances mitochondrial function and proliferation of CD8+ T-cells, synergizing with PD-1 blockade to improve antitumor responses (52). These findings underscore the therapeutic potential of mitochondrial biogenesis enhancement to overcome T-cell exhaustion and metabolic insufficiency within the tumor microenvironment.

Pharmacological agents that activate mitochondrial biogenesis pathways have also been explored. Resveratrol, a natural polyphenol, activates AMPK and stimulates PGC-1α expression, thereby promoting mitochondrial biogenesis and improving muscle regeneration and metabolic function in obesity models (53,54). In T-cells, AMPK activation similarly supports mitochondrial biogenesis and function, which is essential for sustaining T-cell responses under metabolic

stress (22). Other compounds, such as pentoxifylline, have been shown to enhance antioxidative capacity and upregulate PGC-1α and downstream mitochondrial biogenesis factors, improving behavioral deficits associated with aging (55). Furthermore, natural extracts such as ginger extract promote mitochondrial biogenesis and function in tumor-infiltrating $CD8^+$ T-cells, enhancing their cytotoxicity and contributing to tumor growth inhibition (56). These examples highlight the diverse pharmacological strategies to augment mitochondrial biogenesis and thereby potentiate T-cell function.

Mitochondrial biogenesis is also regulated by signaling pathways that integrate environmental cues and cellular stress responses. For instance, the ATM-LARP7-sirtuin 1 axis has been identified as a critical regulator of mitochondrial biogenesis and energy metabolism in cardiac tissue (57); in T-cells an analogous Sirt3-dependent axis sustains oxidative metabolism and memory development (22). Whether the LARP7 arm operates in T-cells has not been tested. In the context of immune cells, platelet factor 4 enhances mitochondrial biogenesis in $CD4^+$ central memory T-cells via the Akt-PGC1α-TFAM pathway, leading to increased proliferation and effector responses (58,59). Similarly, adenosine receptor A1 activation promotes mitochondrial biogenesis through PGC-1α and confers neuroprotection after cerebral ischemia (60). Whether the same axis operates in tumor-infiltrating T-cells has not been tested, and we therefore regard it as a hypothesis rather than an established mechanism. These pathways offer mechanistic insights into how mitochondrial biogenesis can be modulated to improve immune cell function.

In addition to the direct activation of biogenesis pathways, mitochondrial quality control processes, such as mitophagy and mitochondrial dynamics are intertwined with biogenesis to maintain mitochondrial homeostasis. The disruption of this balance can impair T-cell function and promote exhaustion. For example, studies have shown that mitochondrial dysfunction in T-cells is associated with impaired biogenesis and dynamics, contributing to diminished antitumor immunity (49,61). Interventions that restore mitochondrial biogenesis and dynamics, such as through the modulation of C1QBP or Ncoa2, enhance mitochondrial integrity and T-cell activation, thereby improving antitumor responses (61,62).

Taken together, the strategies reviewed in this section fall into two groups whose supporting evidence is of unequal strength. Consistent evidence across murine melanoma models and human T-cells indicates that increasing mitochondrial content through the PGC-1α-NRF1/2-TFAM axis restores oxidative metabolism, improves memory formation and increases antitumor activity (51,52); this conclusion is concordant across independent studies and we regard it as the best supported of the strategies considered here. The evidence for the pharmacological agents is, by contrast, uneven and in part conflicting. Ginger extract has been shown to act on tumor-infiltrating $CD8_+$ T-cells directly (56), whereas the data for resveratrol and pentoxifylline were obtained in muscle regeneration and aging models and in cardiac tissue (53-55,57); in these cases, although the mechanism is plausible, the relevant T-cell population has not been tested, and the findings should not be read as established in T-cells. A further limitation is that the two routes have never been compared directly: To the best of our knowledge, no study has measured the gain in respiratory capacity produced by enforced PGC-1α expression against that produced by a pharmacological activator in the same model. The assessment made herein is therefore that enforced or epigenetically induced PGC-1α is the best supported approach in this section, and that pharmacological activation remains preliminary and requires target-engagement data in tumor-infiltrating T-cells before clinical evaluation (Fig. 2).

4. Redox-directed interventions: Antioxidants and reactive oxygen species

Role of antioxidants. Antioxidants play a crucial role in mitigating mitochondrial damage and improving T-cell function, particularly in the context of tumor immunity where mitochondrial dysfunction contributes significantly to T-cell exhaustion and impaired antitumor responses. Exhausted TILs exhibit defective OXPHOS, mitochondrial depolarization and impaired metabolic adaptation, leading to compromised effector functions. Antioxidants can alleviate these mitochondrial defects by scavenging ROS and restoring redox balance, thereby enhancing mitochondrial integrity and bioenergetics essential for T-cell activation and proliferation. Conversely, some agents that act on mitochondria do so by amplifying rather than by scavenging ROS: icariin promotes mitochondrial dysfunction and ferroptosis in tumor cells and, in doing so, enhances the efficacy of PD-1 blockade (63). Similarly, natural polyphenols like resveratrol and oleuropein improve mitochondrial and proteostasis functions in exhausted CD8 T-cells from chronic hepatitis B patients, enhancing cytokine production and antiviral activity by correcting oxidative stress (64).

In TMEs characterized by excessive ROS, antioxidants help maintain T-cell redox homeostasis, preventing oxidative damage that leads to apoptosis or functional impairment. Hemoglobin α-a1, identified as a mitochondrial-associated antioxidant protein in T lymphocytes, buffers mitochondrial ROS and modulates inflammatory cytokine production, highlighting intrinsic antioxidant mechanisms within T-cells (65). Pharmacological antioxidants such as α-lipoic acid and betulinic acid activate endogenous antioxidant pathways [e.g., nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase (HO)-1], reduce ROS levels and improve mitochondrial function in non-lymphoid tissues (66,67). The same pathway would be expected to protect T-cells from oxidative damage; however, this has not been demonstrated directly in T-cells and remains a testable hypothesis. Moreover, antioxidants restore mitochondrial biogenesis and function through Nrf2, sirtuin 3 (Sirt3) and superoxide dismutase 2 (Sod2) signaling in non-lymphoid cells (68,69); in T-cells, Sirt3-dependent signaling provides a T-cell-intrinsic route to the same outcome by sustaining oxidative metabolism and memory development (22).

Preclinical studies have also suggested that combining antioxidants with immunotherapies can potentiate antitumor responses. For instance, the use of antioxidants alongside ICB or adoptive T-cell therapies can enhance T-cell metabolic fitness, prevent terminal exhaustion and improve cytokine secretion, thereby overcoming immunosuppressive TMEs (70,71). Antioxidants mitigate the oxidative stress-induced inhibition

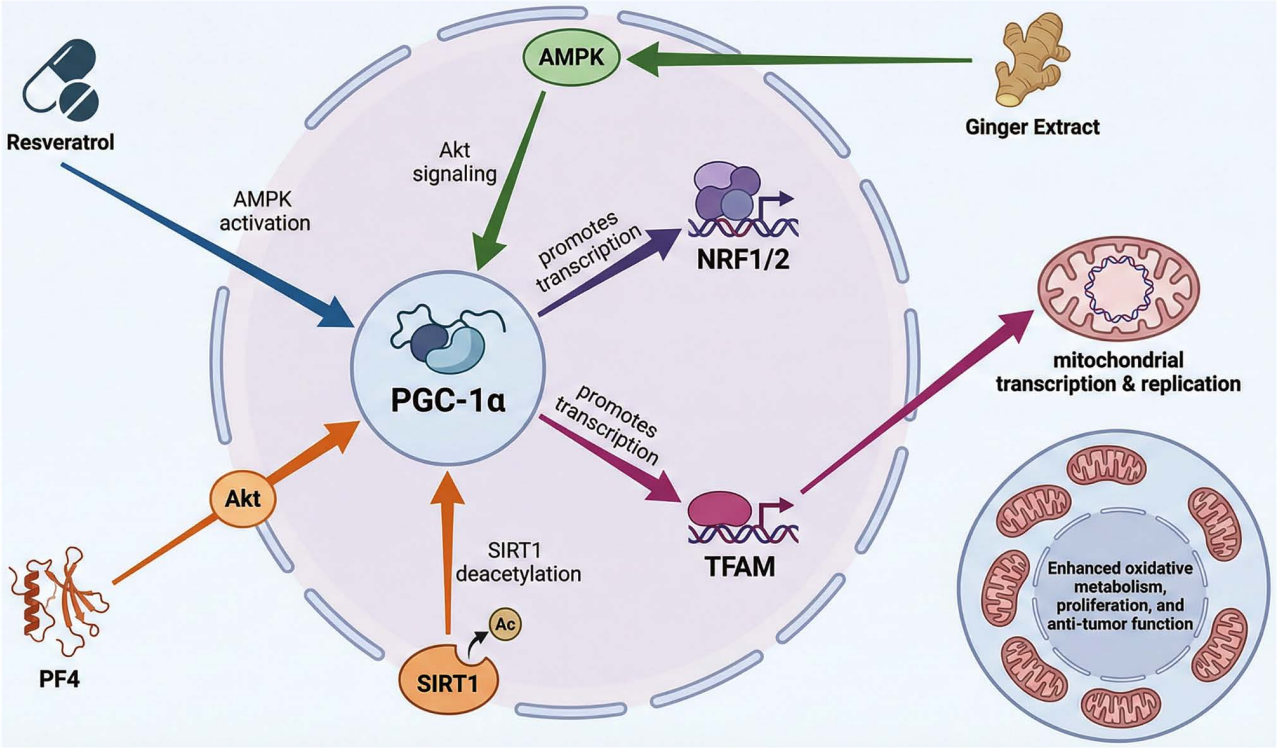


Figure 2. Core regulatory network of mitochondrial biogenesis and strategies for its enhancement. PGC-1α occupies the center of the network and drives transcription of NRF1/2 and of TFAM. TFAM in turn drives mitochondrial transcription and replication, expanding the mitochondrial pool and enhancing oxidative metabolism, proliferation and antitumor function. Four inputs converge on PGC-1α, shown with the agents used experimentally to activate them: Resveratrol and ginger extract act through AMPK activation; PF4 acts through Akt; and SIRT1 activates PGC-1α by deacetylation. Akt signaling also feeds directly onto NRF1/2. The key mechanism is the following: The network is a transcriptional cascade. PGC-1α integrates upstream metabolic and stress signals and, through NRF1/2 and TFAM, couples nuclear transcription to mitochondrial replication and to oxidative metabolism. The direction of effect is as follows: All four inputs are shown as positively regulating PGC-1α and downstream biogenesis, and thereby mitochondrial mass and respiratory capacity. The therapeutic implication is the following: The pharmacological activation of this cascade, rather than genetic manipulation, is the route most readily testable in patients. The evidence basis involves enforced and epigenetically induced PGC-1α in murine melanoma models and DNA-based PGC-1α/β activators (51,52); ginger extract in tumor-infiltrating CD8$^+$ T-cells (56); PF4 signaling through Akt-PGC-1α-TFAM in human CD4$^+$ memory T-cells (58,59). Two of the inputs rest on indirect evidence: the resveratrol and pentoxifylline data derive from muscle regeneration and aging models, and the ATM-LARP7-SIRT1 axis from cardiac tissue (53-55,57). The AMPK-Sirt3 route is documented in T-cells (22). Extension of the muscle and cardiac findings to tumor-infiltrating T-cells has not been tested and is presented here as a hypothesis. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; NRF1/2, nuclear respiratory factor 1/2; TFAM, mitochondrial transcription factor A; PF4, platelet factor 4; SIRT1, sirtuin 1; AMPK, AMP-activated protein kinase; Sirt3, sirtuin 3.

of key metabolic enzymes and signaling pathways (e.g., glycolysis and STAT3 phosphorylation), which are essential for T-cell differentiation and function (72). Additionally, antioxidant strategies can reduce immunosuppressive Treg populations and myeloid-derived suppressor cells, further enhancing antitumor immunity (73).

Clinical data on antioxidants in patients with cancer remain limited and mixed. Interventions administered around the time of cancer surgery have been associated with reduced oxidative-stress markers and lower levels of inflammatory cytokines (74); however, as discussed below, no antioxidant strategy has yet improved outcomes in unselected patients, and one randomized trial was terminated. Furthermore, natural compounds with antioxidant properties, such as polysaccharides from traditional Chinese medicine, have been shown to modulate gut microbiota and systemic immunity, contributing to enhanced antitumor effects (75,76).

In summary, the antioxidants discussed herein reduce the mtROS load, preserve membrane potential and ATP production and modulate redox-sensitive signaling, and in the models examined, this improves T-cell survival and effector function. The evidence for these effects is, however, of unequal strength, and the distinction matters for how the strategy should be pursued. The observations made directly in T-cells, the redox-sensitive mitochondrial protein hemoglobin α-a1 in human T-lymphocytes (65) and the restoration of exhausted CD8$^+$ T-cells from patients with chronic hepatitis B by polyphenol treatment (64), are the most directly relevant, and the Sirt3-dependent route is documented in T-cells as well (22). By contrast, the Nrf2/HO-1 and Nrf2/Sirt3/Sod2 data for α-lipoic acid and betulinic acid derive from non-lymphoid tissues (66-69), and their extension to tumor-infiltrating T-cells has yet not been tested. Therefore, the intrinsic antioxidant machinery expressed by T-cells can be regarded as the better supported target in this subsection, and the pharmacological antioxidants as preliminary; whether redox modulation can be delivered beneficially to patients is addressed below (Fig. 3).

Dual role of ROS. ROS are chemically reactive molecules derived from oxygen that play a pivotal role in modulating immune cell functions, including T-cells. In the context of T-cell biology, ROS function as critical signaling molecules that influence T-cell activation, differentiation, proliferation and effector functions. Mitochondria are a major source of

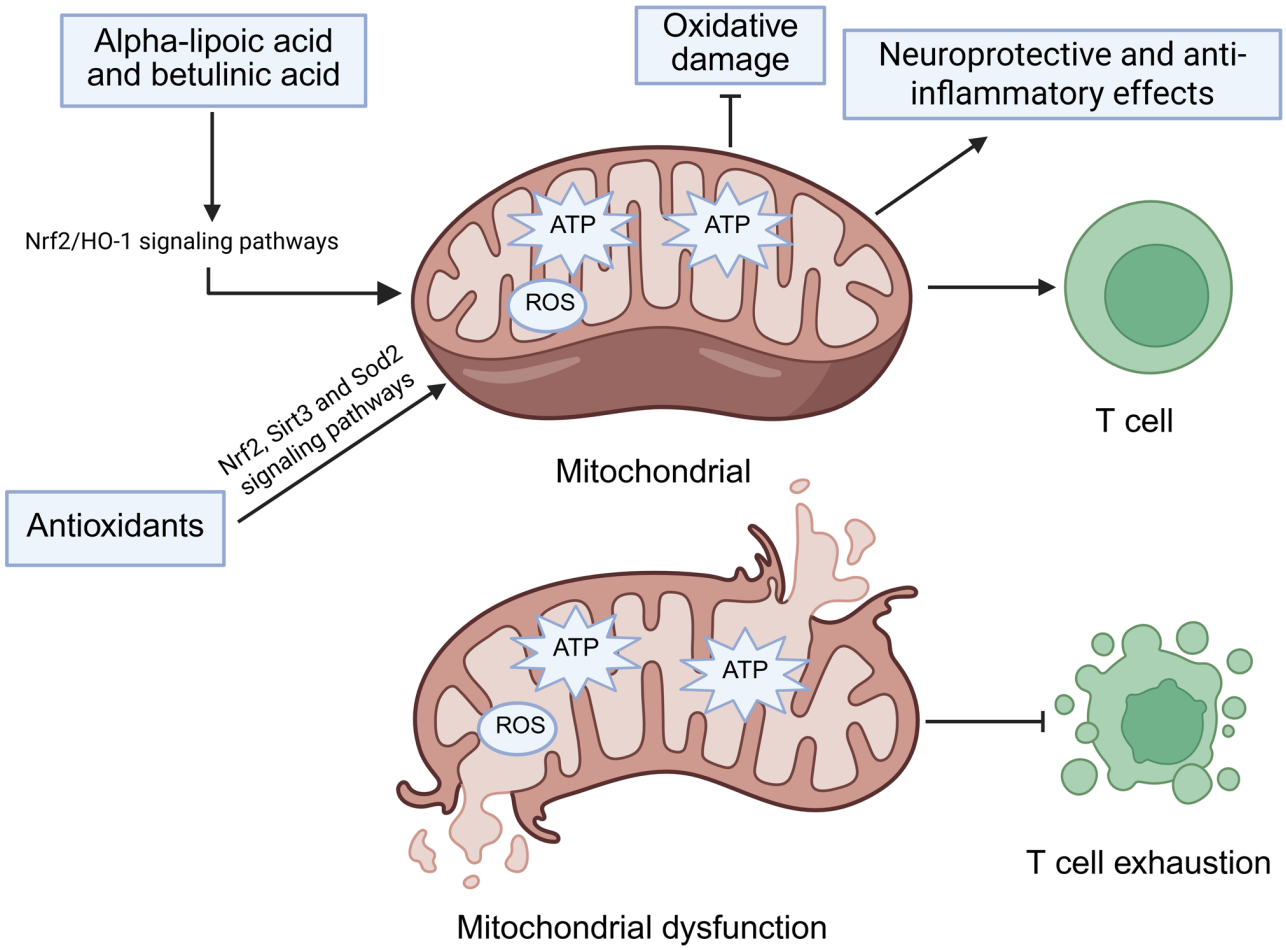


Figure 3. Mechanisms by which antioxidants reduce mitochondrial injury in T-cells. Two states are contrasted. In the top panel, an intact mitochondrion generating ATP while maintaining low levels of ROS is shown; antioxidants act through two signaling routes, α-lipoic acid and betulinic acid through Nrf2/HO-1, and other antioxidants through Nrf2, Sirt3 and Sod2, and oxidative damage is shown as an inhibitory input onto the mitochondrion. In the bottom panel, a mitochondrion with damaged, leaky cristae and unrestrained ROS release is shown, which exerts an inhibitory effect on T-cells and drives the fragmented phenotype of T-cell exhaustion. The key mechanism is the following: Antioxidants act by two routes: The activation of endogenous antioxidant transcription through Nrf2/HO-1, and the activation of the Nrf2/Sirt3/Sod2 axis; both reduce mitochondrial ROS and preserve membrane potential and ATP production. When these pathways fail, ROS escape from the organelle and inhibit T-cell function. The direction of effect is as follows: Antioxidant signaling is protective and restores mitochondrial integrity; unrestrained oxidative damage is inhibitory and promotes exhaustion. The therapeutic implication is as follows: Redox modulation is likely to be beneficial only within a defined window. Untargeted antioxidants scavenge the low-level ROS that T-cell receptor signaling requires, as well as the excess ROS that cause damage, and clinical experience with broad-spectrum antioxidants has been inconsistent or adverse (discussed above in the section 'Dual role of ROS', and in Table III). The evidence basis is the following: The figure combines evidence of unequal strength. Hemoglobin α-a1 as a redox-sensitive mitochondrial protein in human T-lymphocytes (65) and polyphenol treatment of exhausted $CD8^+$ T cells from patients with chronic hepatitis B (64) are T cell-based. Mitochondria-targeted antioxidants have shown benefit in preclinical models (63). By contrast, the Nrf2/HO-1 and Nrf2/Sirt3/Sod2 data for α-lipoic acid and betulinic acid derive from studies in non-lymphoid tissues (66-69); the same pathway would be expected to protect T-cells; however, this has not been demonstrated directly and remains a testable hypothesis. In T-cells, the Sirt3-dependent route is documented (22). A randomized trial of N-acetylcysteine in ovarian and endometrial cancer was terminated (Table III; NCT02569957). ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; Sirt3, sirtuin 3; Sod2, superoxide dismutase 2.

ROS in T-cells, and mtROS serve as second messengers to regulate various immune responses (24). The balance of ROS within T-cells is tightly controlled; while excessive ROS generation can cause oxidative damage and cell death, moderate ROS levels are essential for proper T-cell receptor (TCR) signaling and downstream activation pathways (77,78). For example, ROS regulate phosphorylation cascades and transcription factors that govern T-cell activation and cytokine production (79). Moreover, ROS influence the metabolic reprogramming of T-cells, supporting the energetic and biosynthetic demands during activation and effector differentiation.

Moderate ROS generation promotes antitumor T-cell efficacy by facilitating mitochondrial function and signaling pathways necessary for T-cell cytotoxicity. It has been demonstrated that enhancing mtROS production in T-cells can augment their proliferation and effector functions, thereby improving antitumor immunity (80); in liver tissue, by contrast, NOX4-dependent mitochondrial ROS signaling forms part of a protective antioxidant defense (81), illustrating that the consequences of mitochondrial ROS are tissue- and context-dependent. For instance, the mitochondria-targeting dihydroartemisinin derivative induces mtROS, leading to immunogenic cell death (ICD) and robust $CD8^+$ T-cell responses against tumors (82). Similarly, nanoplatforms that amplify ROS production in tumor mitochondria enhance dendritic cell maturation and T-cell activation, boosting

antitumor immune responses (83,84). The generation of ROS also triggers endoplasmic reticulum stress and the release of DAMPs, which further stimulate adaptive immunity (85). Furthermore, ROS-mediated signaling can activate the cGAS-STING pathway, enhancing type I interferon responses critical for T-cell priming (86).

Notably, ROS levels modulate the balance between T-cell activation and exhaustion, and the distinction between the two is a matter of threshold rather than of molecular identity. At low, transient and spatially confined concentrations, mtROS function as second messengers in T-cell receptor signaling. At higher concentrations, and particularly when production from complexes I and III is sustained, they oxidize cardiolipin, damage mitochondrial DNA and impair OXPHOS, thereby driving the depolarized phenotype characteristic of terminal exhaustion (87). Which outcome predominates therefore depends on concentration, duration and the subcellular site of production, a point that is frequently lost when ROS are discussed as a single entity. This threshold model also provides the most plausible explanation for a discrepancy that recurs in the clinical literature: mitochondrial-targeted antioxidants have repeatedly improved T-cell function in preclinical models, whereas broad-spectrum antioxidant supplementation in patients has produced inconsistent or even adverse results (88). Three non-exclusive explanations deserve testing. First, untargeted antioxidants scavenge the low-level ROS required for T-cell receptor signaling, as well as the excess ROS that cause damage, whereas mitochondria-targeted agents, such as MitoQ accumulate at the organelle of origin and are therefore more selective. Second, timing matters: In animal models, the benefit of redox intervention is generally observed when it is administered early, before the exhausted phenotype is epigenetically fixed, whereas patients are usually treated after exhaustion is established. Third, scavenging ROS may be counterproductive when ROS are the intended effector mechanism, as in sonodynamic and photodynamic approaches that deliberately generate mitochondrial ROS to trigger immunogenic cell death. The dual role of ROS is thus regarded as established; however, the therapeutic window within which redox modulation is beneficial remains poorly defined and is, perhaps, the most critical unresolved question in this area (89,90).

Taken together, this section supports two conclusions and leaves one question unresolved. First, the dual role of ROS in T-cells is established rather than hypothetical: Low, transient and spatially confined concentrations of mtROS are required for T-cell receptor signaling and effector function, whereas sustained production at higher concentrations impairs OXPHOS and drives terminal exhaustion (24,77-81,87). Second, redox modulation is the clearest example of conflicting evidence in this field. Mitochondria-targeted antioxidants have produced reproducible benefit in preclinical models (63), whereas broad-spectrum antioxidant supplementation in patients has been ineffective or harmful, and a randomized trial of N-acetylcysteine was terminated (Table III; NCT02569957). The discrepancy is explicable by three non-exclusive factors: The selectivity of the antioxidant, the timing of administration relative to the establishment of exhaustion, and interference with ROS that are the intended effector mechanism; therefore, the therapeutic window for redox modulation rather than the principle itself, is regarded as the unresolved question. From the available evidence, mitochondria-targeted agents are better supported than untargeted antioxidants, which do not warrant further evaluation in unselected patients; no registered trial combines a mitochondria-targeted antioxidant with a checkpoint inhibitor, and this is the most tractable next step (Fig. 3).

5. Mitochondrial transfer and mitochondria-directed agents

Intercellular mitochondrial transfer. Intercellular mitochondrial transfer represents a novel and compelling mechanism by which cells can modulate their metabolic state and function through the horizontal exchange of mitochondria (91,92). This process has garnered increasing attention due to its potential to restore or enhance cellular bioenergetics, particularly in cells with compromised mitochondrial function, such as exhausted T-cells in the TME (93). Mitochondria, traditionally viewed as static intracellular organelles responsible for ATP production and metabolic regulation, are now recognized to be dynamic entities capable of translocating between cells via multiple pathways. These include tunneling nanotubes, extracellular vesicles, gap junctions and direct T-cell-cell fusion (94). The transfer of healthy mitochondria from donor cells to recipient T-cells with impaired mitochondrial function can improve the metabolic fitness of recipient T-cells by replenishing mitochondrial content and restoring OXPHOS capacity (91). Experimental models have demonstrated that such mitochondrial transfer can enhance the bioenergetic profile of T-cells, thereby augmenting their proliferative and effector functions. For instance, bone marrow stromal cells have been shown to form nanotubular connections with $CD8^+$ T-cells, facilitating the direct transfer of mitochondria, which leads to increased mitochondrial respiration and spare respiratory capacity in recipient T-cells. This metabolic reprogramming translates into improved T-cell expansion, tumor infiltration and reduced exhaustion, culminating in superior antitumor efficacy *in vivo* (91). The molecular underpinnings of mitochondrial transfer involve cytoskeletal elements, such as F-actin and regulatory proteins, including Talin 2, which are essential for the formation and stabilization of intercellular conduits (92). Additionally, the expression of connexin 43 in mesenchymal stromal cells has been implicated in mediating mitochondrial transfer to chondrocytes, highlighting the importance of specific molecular mediators in this process (94). The transferred mitochondria are not only structurally integrated but also functionally competent, maintaining membrane potential and contributing to enhanced aerobic metabolism in recipient T-cells. Beyond the direct metabolic benefits, mitochondrial transfer can modulate immune responses by suppressing pro-inflammatory cytokine production. Visualization techniques employing fluorescent protein tagging have been pivotal in elucidating the dynamics of mitochondrial transfer, enabling real-time tracking of mitochondria trafficking between donor and recipient T-cells. While the precise initiation signals and regulatory pathways governing mitochondrial transfer remain incompletely understood, oxidative stress and mitochondrial damage in recipient T-cells appear to serve as key triggers that promote the formation of intercellular connections and organelle exchange. Of note, mitochondrial transfer is bidirectional

Table III. Registered clinical trials of mitochondria- or metabolism-directed agents combined with immune checkpoint inhibitors.

Agent or strategy	Combination	Tumor type	Phase	Status (September 27, 2026)	Registration
Metformin	Pembrolizumab	Advanced melanoma	Phase 1	Active, not recruiting	NCT03311308
Metformin	Nivolumab	Refractory MSS colorectal cancer	Phase 2	Completed	NCT03800602
Metformin	Durvalumab	Head and neck squamous cell carcinoma	Early phase 1	Completed	NCT03618654
Metformin	Nivolumab	Recurrent non-small cell lung cancer	Phase 2	Status unknown	NCT03048500
Metformin	Sintilimab	Non-small cell lung cancer	Phase 2	Status unknown	NCT03874000
Metformin	PD-1 inhibitor	Small-cell lung cancer	Phase 2	Status unknown	NCT03994744
Metformin (with or without rosiglitazone)	Nivolumab or pembrolizumab	Melanoma; NSCLC; hepatocellular carcinoma	Phase 2	Recruiting	NCT04114136
Metformin	Standard-of-care chemotherapy and/or immunotherapy	Advanced solid tumors	Phase 1	Recruiting	NCT07098299
Metformin	Chemoimmunotherapy	Diffuse large B-cell lymphoma	Phase 2	Terminated	NCT02531308
CB-839 (glutaminase inhibitor)	Nivolumab	Clear cell renal cell carcinoma	Phase 1/2	Terminated	NCT02771626
N-acetylcysteine	Topotecan-based therapy	Ovarian and endometrial cancer	Phase 2	Terminated	NCT02569957
Engineered mitochondrial vaccine (IMP3-Mito)	PD-1 inhibitor	Resectable head and neck squamous cell carcinoma	Phase 2	Recruiting	NCT07572864

PD-1, programmed death 1.

and context-dependent; for example, in the TME, cancer cells can 'hijack' mitochondria from immune cells, thereby enhancing their own metabolic fitness and contributing to immune evasion (93). Conversely, therapeutic strategies aimed at supplying healthy mitochondria to exhausted T-cells hold promise for restoring antitumor immunity. Collectively, these findings underscore the critical role of intercellular mitochondrial transfer in modulating T-cell metabolism and function, offering a novel avenue for enhancing immunotherapeutic efficacy by targeting mitochondrial dynamics and intercellular organelle trafficking (91-97) (Fig. 4).

Mitochondria-directed agents and delivery platforms. Mitochondria have emerged as pivotal therapeutic targets across a broad spectrum of diseases, including cancer, metabolic disorders, neurodegenerative diseases and immune dysfunctions. Their central role in cellular energy metabolism, calcium homeostasis, apoptosis regulation and ROS generation renders them attractive for intervention. In cancer therapy, mitochondria-targeted strategies exploit the altered mitochondrial metabolism and dynamics characteristic of tumor cells to induce cell death and overcome drug resistance (98). Various approaches include the use of mitochondria-targeted small molecules, metal complexes, nanomedicines and phototherapeutic agents (99-110). For instance, mitochondria-targeting organic sensitizers have been developed to induce regulated cell death modalities, such as apoptosis, ICD, ferroptosis, pyroptosis and autophagy, thereby eliciting antitumor immune responses through the release of DAMPs (99). Nanoparticle-based delivery systems have been engineered to enhance selective drug accumulation in mitochondria, improving therapeutic efficacy and reducing systemic toxicity. These include polymeric nanoparticles, liposomes, metal-organic frameworks and novel nanoplatforms that facilitate mitochondrial targeting via ligands, such as triphenylphosphonium (TPP) or mitochondria-penetrating peptides (100,101). Photodynamic and photothermal therapies leveraging mitochondria-targeted photosensitizers have shown promise in amplifying ROS production within mitochondria, triggering mitochondrial dysfunction and subsequent cancer cell death (102,103). Furthermore, mitochondria-targeted chemodynamic therapies and sonodynamic therapies have been enhanced by nanodrug

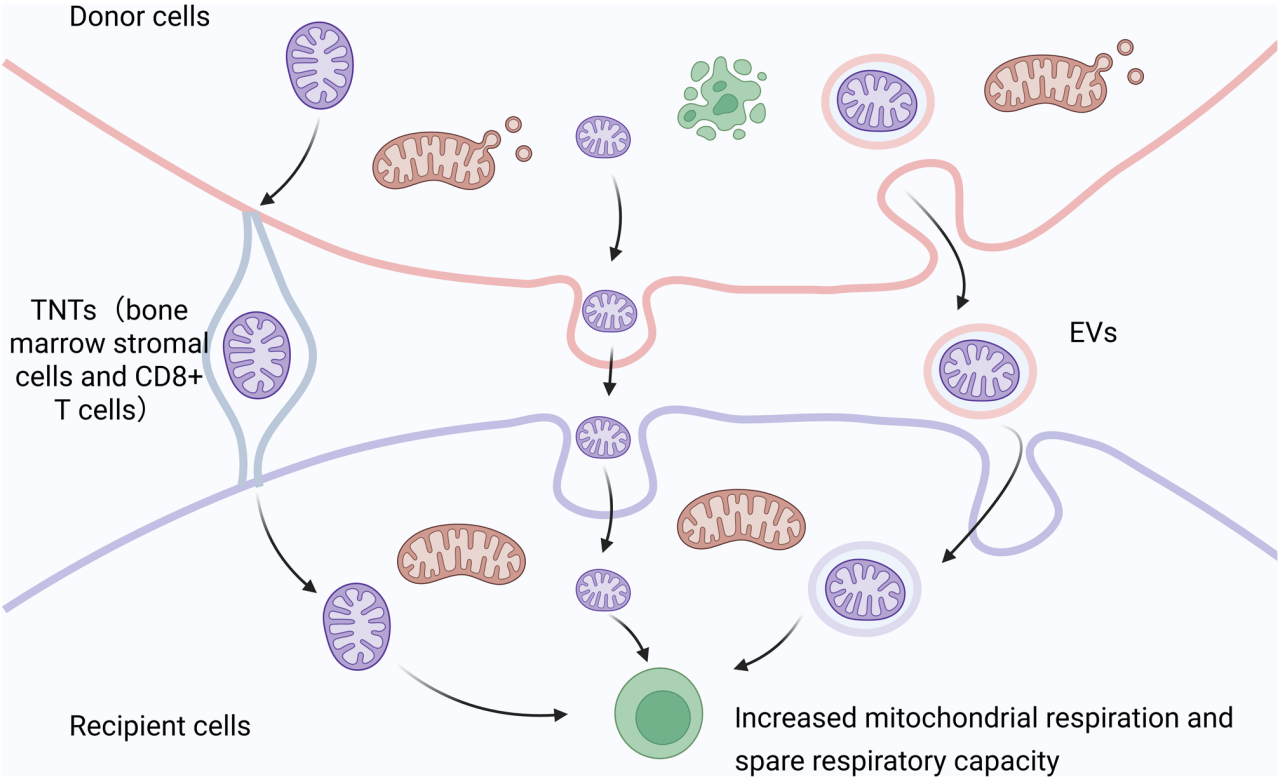


Figure 4. Routes of intercellular mitochondrial transfer and the metabolic consequence for the recipient cell. Donor cells (top panel) release intact mitochondria that are taken up by recipient cells (bottom panel) by two principal routes: TNTs, shown as a conduit between bone marrow stromal cells or CD8$^+$ T-cells and the recipient, and EVs, shown as mitochondria enclosed within vesicles. Mitochondria in transit are shown in purple, distinct from the resident mitochondria of the recipient. The key mechanism is the following: Transferred mitochondria replenish mitochondrial content in the recipient and restore oxidative phosphorylation capacity; connexin 43 is implicated in the formation of the transfer conduit, and nanotube-mediated transfer has been shown to enhance T-cell metabolic fitness. The direction of effect is as follows: Transfer is shown as positively regulating the bioenergetic state of the recipient cell. The therapeutic implication is the following: Allogeneic mitochondria could in principle be supplied as an off-the-shelf metabolic therapy, but the approach remains preclinical and faces unresolved problems of dose, purity and selectivity. The evidence basis is as follows: All evidence depicted is preclinical. Nanotube-mediated transfer enhancing T-cell metabolic fitness (91); mesenchymal stromal cells as donors (96); connexin 43 in non-lymphoid recipient cells (94); reviews of transfer biology and of mitochondria in tumor progression (92,93,97). No registered trial delivers mitochondria to T-cells (Table III). TNTs, tunneling nanotubes; EVs, extracellular vesicles.

designs that localize ROS generation to mitochondria, overcoming limitations of ROS diffusion and improving antitumor efficacy (104,105). In immunotherapy, mitochondrial regulation is crucial for reversing T-cell exhaustion and enhancing antitumor immunity, with mitochondria-targeted interventions restoring T-cell function and boosting ICB responses (111). Additionally, mitochondria-targeted agents can modulate the TME by inducing immunogenic cell death and enhancing dendritic cell activation, thereby improving the efficacy of combined immunotherapies (112,113). Engineered cell products provide an additional route: The enforced expression of PGC-1α increases mitochondrial content and oxidative metabolism and improves the persistence and antitumor function of CD8$^+$ T-cells (51), and mitochondrial metabolism is a determinant of chimeric antigen receptor (CAR) T-cell exhaustion and function (70,114), which renders mitochondrial engineering an attractive modification for adoptive cell products (Fig. 5). The potential of mitochondria as drug targets extends beyond cancer, with therapeutic strategies aimed at mitochondrial dysfunction showing promise in metabolic diseases, neurodegeneration, kidney injury, and ischemic conditions by restoring mitochondrial bioenergetics and reducing oxidative stress (115-118). Collectively, these advances underscore mitochondria as versatile and potent therapeutic targets, with mitochondria-targeted therapies offering opportunities for precision medicine through improved selectivity, efficacy, and immunomodulation.

Translational barriers to mitochondrial targeting. Whether mitochondria-directed agents act on tumor cells, on T-cells, or on both determines whether they are likely to help or to harm. This question of selectivity is more consequential than the catalog of delivery chemistries through which it is achieved. TPP conjugates, mitochondria-penetrating peptides, metal-organic frameworks and polymeric carriers all exploit the mitochondrial membrane potential to concentrate cargo in the organelle (106-108). That potential is, however, shared by tumor cells and by activated T-cells, so that the same nanoplatform that kills tumor cells through mitochondrial disruption may also compromise the T-cells on which checkpoint blockade depends. In practice, the two populations differ in ways that can be exploited. Tumor mitochondria are frequently hyperpolarized and more dependent on OXPHOS, whereas effector T-cells in the TME are more often depolarized and metabolically constrained; the route of administration also provides a further degree of control, since intratumoral delivery spares

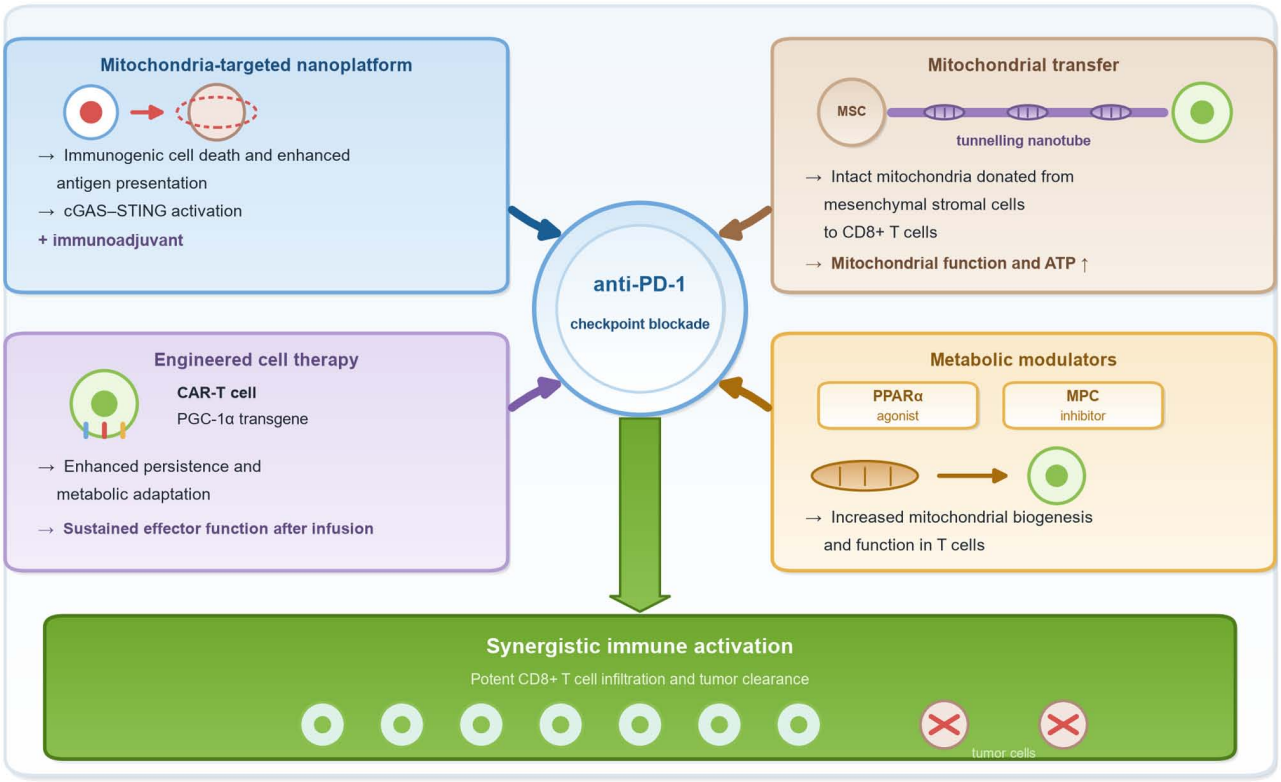


Figure 5. Mitochondria-directed strategies that converge on checkpoint blockade: Platform categories and the resulting antitumor response. Anti-PD-1 forms the central axis, with four mitochondrial strategies acting in parallel. The upper left panel illustrates mitochondria-targeted nanoplatforms, in which a photodynamic therapy agent generates mitochondrial reactive oxygen species within tumor cells, driving immunogenic cell death, enhanced antigen presentation and activation of the cGAS-STING pathway. The upper right panel illustrates mitochondrial transfer, in which mesenchymal stromal cells donate mitochondria to $CD8^+$ T-cells through tunneling nanotubes. The lower left panel illustrates engineered cell therapy, in which PGC-1α is overexpressed in T-cells to increase oxidative metabolism and persistence. The lower right panel illustrates metabolic modulators, in which PPARα agonists act on T-cells to increase mitochondrial biogenesis and function. In the bottom panel, the combined effect shown is synergistic immune activation, with $CD8^+$ T-cell infiltration and tumor clearance. The key mechanism is the following: Four distinct mitochondria-directed platforms converge on the same effector step: each increases mitochondrial function, reactive oxygen species-dependent immunogenicity or mitochondrial transfer in a different cell population, and each is shown acting alongside, rather than instead of, checkpoint blockade. The direction of effect is as follows: All four platforms are shown as positively regulating checkpoint-blockade-induced antitumor immunity. The therapeutic implication is the following: The figure maps the platform classes by stage of development: nanoplatforms and mitochondrial transfer are preclinical, PPARα agonists have animal-model support alongside an active clinical program, and an engineered mitochondrial vaccine is under clinical evaluation. The evidence basis is as follows: Nanoplatform, photodynamic and cGAS-STING data are preclinical (69,82-84); mitochondrial transfer data are preclinical (91,96); PPARα agonist data are from murine models (27); PGC-1α overexpression in T-cells is supported by murine $CD8^+$ T-cell studies (51), and mitochondrial metabolism is an established determinant of CAR T-cell exhaustion and function (70,114). The combination of a PGC-1α transgene with CAR T cells is shown as a proposed strategy, not as a reported result. An engineered mitochondrial vaccine is being tested in a recruiting phase 2 trial (NCT07572864; Table III). Direct clinical evidence of benefit from any of these platforms is not yet available. PD-1, programmed death 1; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PPAR, peroxisome proliferator-activated receptor; MPC, mitochondrial pyruvate carrier.

circulating lymphocytes. Photodynamic and photothermal platforms add spatial selectivity because activation requires local illumination (109,110). Even so, the majority of published platforms have been characterized for tumor-cell cytotoxicity and have not been tested for their effect on tumor-infiltrating T-cell function (99-108). The therapeutic index of these agents in an immunocompetent, immunotherapy-treated host is therefore largely unknown. This is considered the principal gap between the chemistry of mitochondrial targeting and its clinical usefulness.

Despite significant progress being made, several challenges remain in translating mitochondria-targeted therapies into clinical practice. One major hurdle is achieving the selective and efficient delivery of therapeutic agents to mitochondria within target T-cells while minimizing systemic toxicity. The complex double-membrane structure and dynamic nature of mitochondria necessitate sophisticated delivery systems, such as mitochondria-targeted nanoparticles, liposomes, and conjugates with mitochondriotropic ligands such as TPP or mitochondrial-penetrating peptides. Future research is required to focus on optimizing these delivery platforms to enhance specificity, stability and controlled release profiles. Additionally, understanding the heterogeneity of mitochondrial function across different T-cell types and disease states is critical for designing tailored therapies. The TME poses additional challenges, including hypoxia, acidic pH and immunosuppression, which can affect mitochondrial targeting and drug efficacy. Integrating mitochondrial targeting with immunomodulatory strategies holds promise, as mitochondria play key roles in immune cell activation and exhaustion; thus, combinatorial approaches with ICIs or adoptive cell therapies may improve outcomes. Moreover, the safety profile and long-term biocompatibility of mitochondria-targeted agents require thorough evaluation, particularly for metal-based

complexes and nanomaterials, to mitigate potential off-target effects and toxicity. Advances in synthetic biology, nanotechnology, and computational modeling are expected to facilitate the design of smart, stimuli-responsive mitochondria-targeted therapeutics capable of adapting to the TME and achieving precise spatiotemporal control. Clinical trials are warranted to validate preclinical findings and establish dosing regimens, pharmacodynamics, and efficacy in diverse patient populations. Furthermore, expanding the application of mitochondria-targeted therapies beyond oncology to metabolic, neurodegenerative, and inflammatory diseases represents a fertile area for future investigation. Overall, the integration of multidisciplinary approaches and continued mechanistic insights will be essential to realize the full clinical potential of mitochondria as therapeutic targets.

In conclusion, the two approaches reviewed in this section are mechanistically distinct but share the same evidential limitation. Mitochondrial transfer restores bioenergetic capacity in the recipient T-cell, and nanotube-mediated transfer has been shown to enhance T-cell metabolic fitness and antitumor activity; these findings are concordant across donor cell types and recipient systems (91-94,96,97). The mitochondria-directed agents and delivery platforms constitute a large and rapidly growing chemistry whose value in the context of immunotherapy is, by contrast, unproven: the overwhelming majority of the platforms listed in the section 'Mitochondria-directed agents and delivery platforms' above were assessed against tumor cells, and their effect on the T-cell compartment that checkpoint blockade depends upon remains largely unmeasured (99-113,115-118). Neither route has been tested in patients in combination with checkpoint blockade and the unresolved question is common to both, selectivity, since the delivery strategies exploit a membrane potential that is not specific to tumor cells, as discussed above (106-108). From the current evidence, both approaches should be described as preclinical. Mitochondrial transfer is the more immediate candidate for a first-in-human study, as the intervention is biological rather than chemical and its selectivity can be addressed through the choice of donor and recipient populations; the nanoplatform strategies require a selectivity solution before they can be tested in patients (Figs. 4 and 5).

6. Combination with immune checkpoint inhibitors: Evidence and clinical translation

Mechanisms of action of ICIs. ICIs have revolutionized cancer therapy by blocking inhibitory pathways, such as cytotoxic T-lymphocyte-associated protein 4 and the PD-1/programmed death-ligand 1 (PD-L1) axis that suppress T-cell activation, thereby reinvigorating antitumor immunity primarily mediated by $CD8^+$ T-cells (119). These monoclonal antibodies unleash T-cell cytotoxicity against tumor cells; however, there are certain limitations, including incomplete response rates and immune-related adverse events (irAEs) (119,120). The efficacy of ICIs depends not only on TCR signaling, but also on the metabolic fitness and mitochondrial function of T-cells within the TME (121,122). Mitochondria regulate T-cell bioenergetics, ROS production and apoptotic signaling, all critical for sustaining effector function and proliferation. Exhausted T-cells in tumors often display mitochondrial dysfunction, which impairs their antitumor activity and limits ICI efficacy (123,124).

Combining ICIs with mitochondrial-targeted therapies aims to restore or enhance mitochondrial function in T-cells, thereby overcoming exhaustion and improving immune responses. For example, pharmacological agents such as bezafibrate, a PPAR agonist, have been shown in preclinical models to augment mitochondrial biogenesis and oxidative metabolism in $CD8^+$ T-cells, synergizing with PD-1 blockade to increase ROS production and promote antitumor cytotoxicity (27). Similarly, targeting mitochondrial electron transport chain components can modulate immune checkpoints expression on leukemic cells, reducing immunosuppressive signals and enhancing T-cell-mediated killing (125). Moreover, mitochondrial quality control pathways such as mitophagy in dendritic cells influence antigen presentation and T-cell priming. Modulating these pathways can potentiate PD-1 inhibitor efficacy: The Shen Qi Yi Chang formula enhances dendritic cell mitophagy via the PINK1-Parkin pathway and improves the response to PD-1 blockade in colorectal cancer models (126).

Clinically, combination strategies have shown promising synergistic effects. For instance, the addition of mitochondrial metabolism enhancers or immunostimulatory agents to ICIs improved tumor control and survival in murine models of melanoma and lymphoma (127,128). Hyperthermia, which promotes immune cell infiltration and upregulates PD-L1 expression through mitochondrial signaling pathways, was shown to increase the response rates when combined with ICIs in advanced cancer patients (129). Nanoparticle-based delivery systems carrying TLR7/8 agonists have also demonstrated synergistic antitumor immunity with anti-PD-1 antibodies by activating innate and adaptive immune responses, partly through mitochondrial metabolic reprogramming (121). Furthermore, the combination of ICIs with agents that modulate mitochondrial function in tumor cells or immune cells can reshape the TME, increasing infiltration and activation of cytotoxic T lymphocytes and macrophage repolarization, thereby enhancing the antitumor immune response (122,130).

Notably, mitochondrial dysfunction is implicated not only in limiting ICI efficacy, but also in the development of irAEs, such as myocarditis and pneumonitis, where mitochondrial metabolism and immune cell polarization play key roles (131,132). Thus, mitochondrial-targeted therapies may also help mitigate adverse events by restoring immune homeostasis.

In summary, the mechanistic rationale for combining ICIs with mitochondrial-targeted therapies lies in the restoration and enhancement of mitochondrial metabolism and quality control in immune cells, particularly T-cells and dendritic cells, which are essential for robust antitumor immunity. Clinical and preclinical evidence supports that such combinations can synergistically improve therapeutic efficacy, increase tumor infiltration of effector immune cells, and potentially reduce immune-related toxicities, representing a promising avenue to overcome resistance and optimize cancer immunotherapy outcomes (Fig. 6).

Registered clinical trials of mitochondria-targeted strategies combined with ICIs. Direct evidence of clinical benefit from

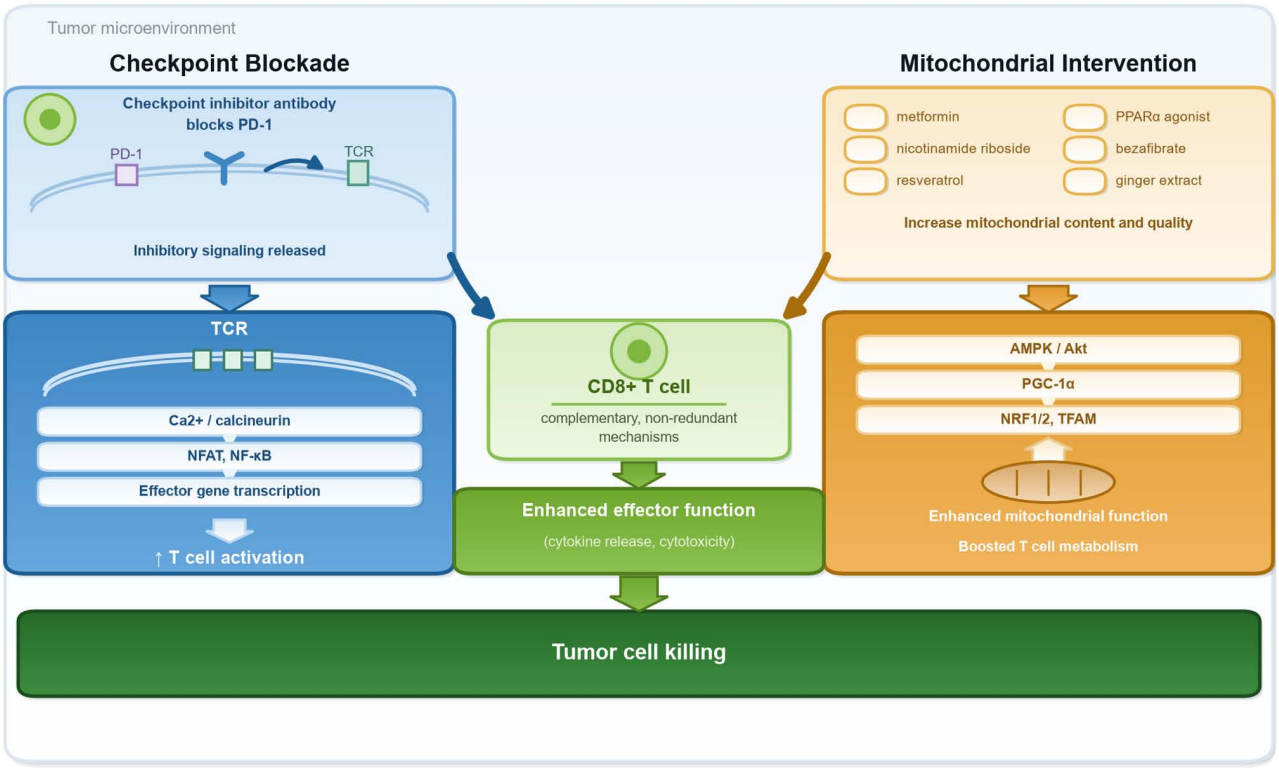


Figure 6. Rationale for combining checkpoint blockade with mitochondrial intervention. Arm 1 (left panel) shows the release of inhibitory signaling by anti-PD-1 or anti-PD-L1 antibodies, which restores T-cell receptor signaling and effector-gene transcription in tumor-infiltrating $CD8^+$ T-cells through calcium-calcineurin signaling and the transcription factors NFAT and NF-κB. Arm 2 (right panel) shows the metabolic arm: Agents that increase mitochondrial content and quality (metformin, PPARα agonists, nicotinamide riboside, bezafibrate, resveratrol and ginger extract) act through AMPK and Akt on PPARα, NRF1/2 and TFAM, increasing mitochondrial biogenesis and mitophagy. The two arms converge on the same cell; below, the restored cell acquires enhanced effector function, and cytokine release and cytotoxicity lead to tumor cell killing. The key mechanism is the following: The two arms act on different nodes of the same effector program. Checkpoint blockade removes an inhibitory signal at the receptor; the metabolic arm restores the bioenergetic capacity required to act on that signal. The direction of effect is as follows: Both arms are shown as positively regulating the same effector program. They are complementary rather than redundant, as checkpoint blockade releases a signal that exhausted T-cells cannot act upon without sufficient mitochondrial capacity. The therapeutic implication is as follows: This provides the mechanistic justification for combining the two classes rather than testing mitochondrial agents as monotherapy (as discussed above in the section 'Mechanisms of action of ICIs'). The evidence basis is the following: Checkpoint-blockade mechanisms from clinical and translational studies (119,120,123,124); the biogenesis arm from animal and mechanistic studies (22,27,51,52); preclinical combination data in murine melanoma and lymphoma (27,127-129). Clinical anchoring is provided by registered trials of metformin with PD-1 or PD-L1 blockade, including a phase 1 study with a pre-specified mitochondrial endpoint (Table III; NCT03311308). Direct clinical evidence that mitochondrial intervention improves immunotherapy outcomes is not yet available. PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PPAR, peroxisome proliferator-activated receptor; AMPK, AMP-activated protein kinase; NRF1/2, nuclear respiratory factor 1/2; TFAM, mitochondrial transcription factor A.

mitochondrial targeting is limited; however, a growing number of registered trials currently address the question. A search of ClinicalTrials.gov on September 27, 2026 identified trials in which a mitochondrial or metabolic agent is combined with an ICI (Table III). The most developed strategy is the addition of metformin, an AMPK activator that promotes mitophagy and improves mitochondrial quality, to PD-1 or PD-L1 blockade. Several trials have been completed or are ongoing across melanoma, non-small cell lung cancer, colorectal cancer and head and neck squamous cell carcinoma. The phase 1 study of pembrolizumab with or without metformin in advanced melanoma (NCT03311308) is of particular relevance to the present review because restoration of mitochondrial function in TILs, assessed by Seahorse metabolic profiling and mitochondrial mass, was a pre-specified secondary endpoint. Metformin has also been combined with nivolumab in refractory microsatellite-stable colorectal cancer (NCT03800602, completed) and with durvalumab in head and neck squamous cell carcinoma (NCT03618654, completed), and further phase 2 trials in lung cancer and other solid tumors are registered (NCT03048500, NCT03874000, NCT03994744, NCT04114136 and NCT07098299).

Beyond metformin, the registered landscape is thinner and, of note, includes failures as well as active studies. The trial using the glutaminase inhibitor, CB-839, combined with nivolumab (NCT02771626) was terminated, as was a trial of metformin with chemoimmunotherapy in diffuse large B-cell lymphoma (NCT02531308), and a randomized study of N-acetylcysteine in ovarian and endometrial cancer using a topotecan backbone (NCT02569957) was likewise terminated. These outcomes should be read as informative rather than incidental: They are consistent with the view expressed above in the section 'Dual role of ROS' that untargeted or late redox intervention is unlikely to be beneficial, and there is an arguement for biomarker-selected rather than unselected enrollment. At the other end of the spectrum, the most direct test of mitochondrial biology as an immunotherapeutic principle is a recently opened phase 2 trial (NCT07572864). This trial combines an engineered mitochondrial vaccine (IMP3-Mito) with a PD-1 inhibitor as neoadjuvant therapy in resectable head and neck

squamous cell carcinoma, with major pathological response as the primary endpoint. It is emphasized that no trial has yet reported an improvement in overall survival attributable to mitochondrial modulation, and that the positive signal in the completed studies is by and large a signal of biological activity rather than of clinical efficacy. Metformin-ICI combinations should therefore be regarded as hypothesis-testing rather than practice-changing; Table III reports trial status explicitly, including studies that were terminated.

Evidence grading and translational barriers. It is useful to separate what the evidence discussed above supports from what it merely suggests. At the mechanistic level, the requirement for mitochondrial function in effector and memory $CD8^+$ T-cells is firmly established, and there is consistent animal-level evidence that enhancing mitochondrial fitness improves antitumor responses (Table IV). At the translational level, the evidence is much weaker. The pharmacological enhancement of mitochondrial biogenesis has not been tested in patients; the evidence rests on enforced PGC-1α expression and on epigenetic activators in murine models (51,52,124). Mitochondrial transplantation and tunneling-nanotube-mediated transfer remain preclinical, and no registered trial delivers mitochondria to T-cells in patients. Mitochondria-targeted nanoplatforms are similarly preclinical and, as noted above in the section 'Translational barriers to mitochondrial targeting', their therapeutic index against tumor-infiltrating T-cells is largely uncharacterized. The only class in which clinical data exist, and then only for biological activity and safety rather than efficacy, is the modulation of mitochondrial metabolism with metformin in combination with checkpoint inhibitors (Table III).

Three consequences follow for trial design. First, mitochondrial endpoints should be measured in patients rather than inferred. Spare respiratory capacity, mitochondrial mass and mitophagic flux in TILs are feasible read-outs, are already pre-specified in at least one registered study (NCT03311308), and should become routine in this field. Second, enrollment should be biomarker-selected, since the terminated trials described above suggest that unselected redox intervention is unlikely to succeed. Third, as the preclinical benefit of metabolic intervention is consistently timing-dependent, trials should record when the mitochondrial agent is started relative to checkpoint blockade rather than treating the combination as a single intervention. Specific, testable priorities are outlined below.

Taken together, this section yields three conclusions that the individual subsections do not make explicit. First, the strength of the evidence is inversely related to how readily each strategy can be tested in patients: The mechanistic case is secure and the animal-level evidence for metabolic intervention consistent (as discussed in the section 'Evidence grading and translational barriers' above and in Table IV); however, the strategies for which any human data exist are the least molecularly specific (27,126-129). Second, and most consequential for the reader, this section contains the clearest conflicting findings in the review. Metformin combined with checkpoint blockade has completed phase 1 and phase 2 studies that establish safety and biological activity but not efficacy, whereas a glutaminase inhibitor given with nivolumab, a metformin-chemoimmunotherapy combination in diffuse large B-cell lymphoma, and a randomized trial of N-acetylcysteine in ovarian and endometrial cancer were all terminated (Table III; NCT02771626, NCT02531308 and NCT02569957). Together with the section 'Dual role of ROS' above, these outcomes are informative rather than incidental: They point to unselected enrollment and to untargeted or delayed intervention, rather than to an incorrect rationale, as the reasons for failure. Third, the comparison across strategies is consequently sharper than the number of registered trials would suggest. Metformin with checkpoint blockade is the most well supported and the only strategy that is clinically evaluable at present, although it should still be regarded as unproven; pharmacological enhancement of biogenesis through PGC-1α is supported only in animal models (51,52,124); and mitochondrial transfer and mitochondria-directed nanoplatforms remain preclinical, the latter carrying the additional unresolved problem of selectivity against tumor-infiltrating T-cells (section 'Translational barriers to mitochondrial targeting' above). No overall-survival benefit has been attributed to mitochondrial modulation in any trial, and it is against that, rather than against the strength of the mechanism, that the field should be judged.

7. Summary and future directions

What the evidence supports. The literature reviewed herein supports four conclusions, which are best stated in order of the strength of the underlying evidence. First, mitochondrial function is required for the antitumor activity of $CD8^+$ T-cells; this is established by concordant genetic and pharmacological evidence in murine models and is consistent with the human data available from trial correlative studies. Second, mitochondrial dysfunction is a convergent phenotype rather than a single lesion: reduced spare respiratory capacity, depolarization, excessive fission and suppressed mitophagy co-occur in exhausted TILs, and interventions directed at one component usually produce partial and transient benefit. Third, the available strategies differ greatly in maturity. Mitochondrial quality control, and in particular the promotion of mitophagy, is the most pharmacologically accessible node identified to date, in part due to the fact that the relevant compounds are already in clinical use for other indications; mitochondrial transplantation and mitochondria-directed nanoplatforms remain at the proof-of-concept stage. Fourth, the clinical evidence base is thin. Of the strategies reviewed, only metabolic modulation with metformin has been evaluated in registered trials in combination with checkpoint inhibitors, and those trials have to date reported biological activity rather than survival benefit.

Mitochondrial dysfunction in the context of other resistance mechanisms. Presenting mitochondrial dysfunction as the constraint on immunotherapy efficacy would overstate the case. T-cell exhaustion in tumors is driven by at least nine recognized mechanisms acting in parallel: Persistent antigen exposure, sustained inhibitory receptor signaling, the epigenetic fixation of the exhausted state, suppressive metabolites including lactate and kynurenine, immunosuppressive cytokines, hypoxia, regulatory T-cells, myeloid-derived suppressor cells and stromal barriers. Mitochondrial dysfunction interacts with several of these rather than sitting above them. Persistent

Table IV. Summary of mitochondrial intervention strategies, levels of evidence and translational status.

Strategy or agent	Target/ mechanism	Model system	Key read-outs	Level of evidence	Clinical translation status	Known limitations	(Refs.)
Metabolic reprogramming: CD28 costimulation; nicotinamide riboside	Restores mitochondrial mass, membrane potential and oxidative metabolism; NAD+ repletion	Murine tumor models; human T- cells *ex vivo*	Mitochondrial mass; membrane potential; oxygen consumption rate; tumor control	Animal	No registered trial of nicotinamide riboside with ICIs identified	NAD^+ precursors may also support tumor cells; no dose-finding data in patients	(43,133)
Mitochondrial biogenesis: enforced PGC-1alpha expression	PGC-1α/ NRF1-2/TFAM transcriptional program	Murine melanoma (genetic)	Mitochondrial mass; OXPHOS; memory formation; tumor control	Animal (mechanistic)	Not clinically testable as gene transfer	Genetic manipulation not translatable; no pharmacological equivalent of comparable potency	(51,124)
Mitochondrial biogenesis: epigenetic PGC-1 α/β activation	DNA-based activator of PGC-1 α/β	Murine tumor models	Mitochondrial function; proliferation; synergy with PD-1 blockade	Animal	None identified	Delivery and durability in humans unknown	(52)
Mitochondrial biogenesis: bezafibrate	Pan-PPAR agonist driving mitochondrial biogenesis	Murine models	ROS production; cytotoxicity; synergy with PD-1 blockade	Animal	PPAR-directed arms included in NCT04114136	Off-target PPAR effects; comparator data not yet reported	(27)
Redox modulation: mitochondria-targeted antioxidants (MitoQ)	Scavenges ROS at the organelle of origin	Preclinical and translational models	Membrane potential; ATP production; CD8+ T-cell-mediated antitumor immunity	Animal/ translational	No registered ICI combination trial identified	Selectivity and timing unresolved	(63,88)
Redox modulation: broad-spectrum antioxidants (NAC, GSH)	Scavenges cytosolic and mitochondrial ROS non-selectively	Clinical	Redox markers; antitumor immunity	Clinical (terminated)	NCT02569957 terminated	Non-selective scavenging may abolish ROS signaling; administered late relative to exhaustion	(89,90)
Metabolic modulation: metformin	AMPK activation; promotes mitophagy and mitochondrial quality control	Clinical	Mitochondrial restoration in TILs (seahorse, mitochondrial mass); ORR; PFS	Clinical (phase 1-2; biological endpoints)	NCT03311308 active, not recruiting; NCT03800602 and NCT03618654 completed; NCT03048500, NCT03874000, NCT03994744,	No survival benefit reported; timing-dependent in animals; unselected enrollment	(40)

Table IV. Continued.

Strategy or agent	Target/ mechanism	Model system	Key read-outs	Level of evidence	Clinical translation status	Known limitations	(Refs.)
					NCT04114136 and NCT07098299 registered		
Mitophagy enhancement: USP30 inhibition	Deubiquitinase antagonizing Parkin-mediated mitophagy	Murine	Mitophagic flux; mitochondrial fitness; effector function; tumor control	Animal	No USP30 inhibitor in oncological clinical development	T-cell selectivity not established; tumor-cell mitophagy may be host-protective	(40)
Mitophagy enhancement: Urolithin A	PINK1-dependent mitophagy; PGAM5 / beta-catenin/Wnt signaling	Murine; human T-cells *ex vivo*	T memory stem cell frequency; persistence; tumor control	Animal/ translational	No oncology ICI trial identified	No oncology dosing or safety data	(41)
Intercellular mitochondrial transfer from mesenchymal stromal cells	Restores mitochondrial content and OXPHOS via tunneling nanotubes, vesicles or gap junctions	Murine; human cells *ex vivo*	Mitochondrial mass; spare respiratory capacity; expansion; tumor control	Animal	None identified	Scale, purity and GMP manufacture unresolved; transfer can also favor tumor cells	(91-94, 96)
Mitochondria-directed nanoplatforms (TPP conjugates, metal-organic frameworks, photodynamic and sonodynamic platforms)	Membrane-potential-driven accumulation; local ROS generation; immunogenic cell death	Preclinical	Tumor-cell cytotoxicity; immunogenic cell death; dendritic cell maturation	Animal	None identified	Therapeutic index against tumor-infiltrating T cells largely uncharacterized; delivery selectivity	(99-110)
Engineered mitochondrial vaccine (IMP3-Mito) plus PD-1 inhibitor	Mitochondrial platform delivering antigen together with checkpoint blockade	Clinical (phase 2, recruiting; n=9)	Major pathological response	Clinical (recruiting; no results reported)	NCT07572864	Very small, single-center study; results pending	(39)

The levels of evidence (applied throughout the present review) are as follows: Mechanistic: a molecular or cellular mechanism demonstrated in human or murine cells *in vitro* or *ex vivo*. Animal: Demonstrated in an *in vivo* tumor model. Translational: Supported by human patient samples or correlative clinical data. Clinical: Supported by data from registered clinical trials. Where a row draws on more than one level, the levels are separated by a slash. ICI, immune checkpoint inhibitor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1; NRF1/2, nuclear respiratory factor 1/2; TFAM, mitochondrial transcription factor A; OXPHOS, oxidative phosphorylation; PD-1, programmed death 1; ROS, reactive oxygen species; PPAR, peroxisome proliferator-activated receptor; NAC, N-acetylcysteine; GSH, glutathione; AMPK, AMP-activated protein kinase; TILs, tumor-infiltrating lymphocytes; ORR, objective response rate; PFS, progression-free survival; PINK1, PTEN-induced kinase 1; TPP, triphenylphosphonium.

antigen exposure and hypoxia are themselves proximal causes of the metabolic stress that damages mitochondria; inhibitory receptor signaling, notably through PD-1, directly alters mitochondrial morphology and motility; and lactate produced by tumor cells is both a metabolic constraint on T-cells and, depending on context, a substrate that they can use. Conversely, mitochondrial dysfunction contributes to the epigenetic remodeling that stabilizes exhaustion, which means that it can be both consequence and cause. Two practical implications follow: The first is that interventions aimed at mitochondria are unlikely to be sufficient on their own: in the studies reviewed here, mitochondrial modulation was almost always combined with checkpoint blockade, and where it was tested alone the benefit was smaller. The second is that mitochondrial dysfunction may be a more tractable target than several of the alternatives, because it is pharmacologically addressable, whereas antigen persistence and stromal exclusion are not readily druggable. Mitochondrial dysfunction may thus be regarded as one of several determinants of immunotherapeutic resistance, and as a particularly actionable one, rather than as the dominant driver.

Limitations. Several limitations should be acknowledged. The present review is a critical review, not a systematic review. Although the search strategy is stated above, the literature was selected to illustrate mechanisms and strategies rather than to be exhaustive, and no formal risk-of-bias assessment was performed. The evidence base is predominantly preclinical and heterogeneous: studies differ in model system, in the dose and schedule of the mitochondrial agent, in the timing of administration relative to tumor inoculation, and in the definition of the exhaustion phenotype, which makes direct comparison of effect sizes across studies unreliable. Publication bias is likely to be substantial, since negative results of mitochondrial interventions are rarely reported, particularly for nanoplatforms. Species differences are important and often understated: The murine genetic evidence for the roles of OPA1, MFN1/2 and DRP1 derives largely from constitutive or inducible knockout systems, and human T-cells differ in their reliance on oxidative phosphorylation, in mitochondrial mass and in the kinetics of exhaustion. Timing is a further systematic issue: In the majority of animal studies, mitochondrial intervention is administered at or shortly after tumor inoculation, whereas patients receive combination therapy when disease is established, and the preclinical benefit of metformin, for example, is lost when treatment is delayed until tumors are large. Finally, the clinical evidence reviewed herein is limited to registered trials and their reported status; few have reported efficacy results in peer-reviewed form, and positive findings should be regarded as provisional until confirmed prospectively. Although these limitations do not undermine the mechanistic conclusions of the present review, they suggest that the translational claims should be weighed accordingly.

Future directions. Of note, six unresolved issues require answers before mitochondrial targeting can be incorporated into immunotherapy regimens: First, whether mitophagy can be increased selectively in tumor-infiltrating T-cells without increasing it in tumor cells, where the same pathway limits cGAS-STING-dependent immunogenicity. Answering this requires cell-type-specific tools, and the development of T-cell-selective USP30 inhibitors would provide a direct test. Second, the therapeutic window for redox modulation in patients needs to be determined. Specifically, it needs to be determined at what stage of exhaustion antioxidant intervention would cease to be beneficial. It also needs to be determined whether this can be predicted from a measurable biomarker, such as mitochondrial membrane potential in circulating T-cells. Third, there is the issue of whether the fusion-fission balance in human TILs is reversible under checkpoint blockade, and if yes, the time course needs to be determined. Single-cell imaging of mitochondrial morphology in sequential biopsies would answer this. Fourth, whether allogeneic, GMP-grade mitochondria can be delivered to human T-cell products at a scale and purity compatible with adoptive cell therapy. Tunneling-nanotube transfer has been demonstrated in murine systems, but has no clinical equivalent, and this gap remains unaddressed. Fifth, it needs to be determined which mitochondrial read-outs should be adopted as standard. The authors propose spare respiratory capacity and mitochondrial mass measured in TILs. These are already feasible in trial correlative studies and are the most consistent discriminators in the preclinical literature. Sixth, there is the issue of whether the timing of mitochondrial intervention relative to checkpoint blockade determines the outcomes of patients as it does in mice. This is testable with existing agents and may be addressed by randomizing the sequence of administration rather than the agents themselves.

8. Conclusion

In conclusion, mitochondrial function is required for the antitumor activity of $CD8^+$ T-cells, and its loss is a consistent feature of exhausted TILs. The evidence reviewed herein does not support the view that mitochondrial dysfunction is the single constraint on immunotherapy efficacy, and we have deliberately avoided that framing. What the evidence does support is a narrower and more useful claim: Mitochondrial dysfunction is one of several determinants of immunotherapeutic resistance, and it is among the most pharmacologically tractable.

Restoring mitochondrial fitness has shown reproducible benefit in preclinical models, both alone and in combination with checkpoint blockade, and the intervention classes reviewed herein differ substantially in maturity. Mitochondrial quality control, and mitophagy in particular, is the most accessible target as existing compounds can be repurposed; mitochondrial transplantation and mitochondria-directed platforms remain at the proof-of-concept stage. Translation is nonetheless constrained by delivery selectivity, by the therapeutic index of the available agents against TILs, and by the fact that the preclinical benefit of metabolic intervention is strongly timing-dependent.

The complexity of T-cell metabolism and of mitochondrial dynamics means that progress will require collaboration between immunologists, metabolism researchers and oncologists, and that mitochondrial read-outs must be built into trial design rather than added retrospectively. The specific questions that are considered most likely to be informative are set out above.

Targeting mitochondrial pathways therefore offers a mechanistically grounded and experimentally testable route to improving the outcomes of cancer immunotherapy, with the important qualification that its value is most likely to lie in combination with, rather than as a substitute for, existing immunotherapies. Whether that promise is realized will be determined by the results of the trials now under way.

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Authors' contributions

YS and MG wrote the main manuscript text. SM was involved in the curation of data from the literature, and in the writing and preparation of the original draft of the manuscript. HL and JC were involved in the writing, reviewing and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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