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Review

Mitochondria and Tumorigenesis

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Abstract

Mitochondria are essential organelles in eukaryotes, serving as the cellular powerhouse for energy production. Mitochondrial dysregulation plays a pivotal role in disease progression by functioning as a "plasticity hub" that coordinates the dynamic tumor microenvironment. This coordination occurs via multidimensional mechanisms such as metabolic rewiring, bioenergetic flux disruption, stress-responsive signaling, and inter-organellar communication, collectively promoting cancer initiation, dissemination, and therapeutic evasion. The current review summarizes recent advances in understanding mitochondria-driven oncogenesis through these mechanisms, discusses mitochondrial-targeted therapeutic strategies and associated challenges, and aims to establish a cross-scale framework for decoding the multi-dimensional synergy of mitochondrial networks in cancer progression, thereby offering insights for developing innovative precision therapies that integrate metabolic-dynamic-immune interventions.

1. Mitochondrial Biology and Functions

As critical double-membraned eukaryotic organelles, mitochondria contain circular Mitochondrial DNA (mtDNA) that encodes 37 genes essential for oxidative phosphorylation - comprising polypeptides, tRNAs, and rRNAs [1,2]. Beyond their canonical role in bioenergy generation through oxidative phosphorylation (OXPHOS) and the tricarboxylic acid (TCA) cycle-mediated ATP production [3], mitochondria functionally extend to metabolic regulation, biosynthetic precursor generation, Ca^{2+} flux coordination, programmed cell death execution, and cellular signaling modulation (Figure 1) [4,5]. mtDNA mutations demonstrate oncogenic potential [6], particularly in malignancies such as breast [7], ovarian [7], and prostate cancers [8].

Cancer, a complex group of diseases, remains a major global health threat with rising incidence driven by population aging [9]. While molecularly-targeted agents and immune checkpoint inhibitors have revolutionized oncology, persistent obstacles including intratumoral heterogeneity, modality-specific constraints, and treatment refractoriness continue to impede clinical success. Consequently, the development of resilient treatment strategies represents an urgent unmet need. This work aims to establish a cross-scale framework elucidating mitochondria-driven multidimensional networks in cancer progression, while exploring innovative therapeutic strategies derived from these insights.

Functioning as a metabolic and signaling nexus, mitochondria establish multidimensional networks through metabolic plasticity, dynamic remodeling, epigenetic regulation, and immune microenvironment reprogramming, acting as an "adaptive engine" that drives malignant transformation, metastasis, and therapeutic resistance (Figure 1). Nevertheless, therapeutic development faces substantial barriers, with mitochondrial-directed compounds frequently demonstrating constrained clinical utility owing to pathway redundancy and tumor cell-intrinsic adaptive mechanisms [10].

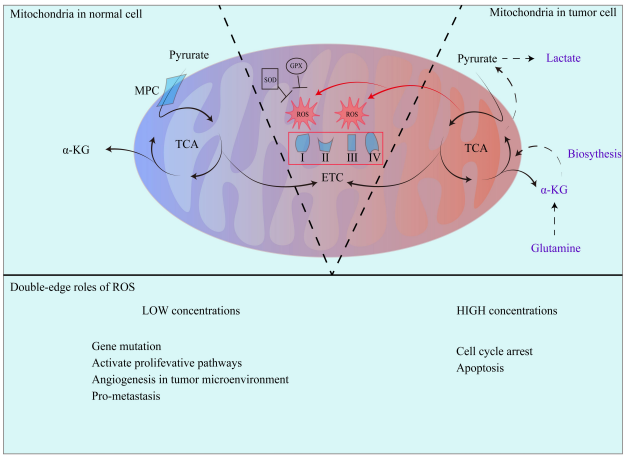

Figure 1. Mitochondrial Metabolic biology in Normal or Cancer Cell.

2. Mitochondrial Metabolic Reprogramming and Cancer

Mitochondrial metabolic reprogramming, characterized by profound functional alterations in cancer, serves as a central driver of malignant progression. By establishing dynamic, collaborative metabolic networks that transcend conventional energy metabolism frameworks,

it achieves multidimensional integration of energy production, redox regulation, and biosynthetic support - mechanisms fundamentally linked to carcinogenesis, metastasis, and therapeutic resistance [11,12]. Distinct from the metabolic homeostasis of normal cells, cancer cells develop spatiotemporally regulated metabolic plasticity through dynamic pathway switching and metabolite functional expansion, forming an adaptable metabolic ecosystem. This system not only fulfills the bioenergetic demands of rapid proliferation but also remodels the microenvironment, modulates immune responses, and drives metastasis/drug resistance through metabolic intermediates, ultimately securing survival advantages in heterogeneous microenvironments. Deciphering the functional modularity and interaction mechanisms within metabolic networks will provide novel perspectives for targeting metabolic vulnerabilities and overcoming therapeutic resistance.

2.1 Dynamic Equilibrium of Energy Metabolism

The malignant proliferation of tumor cells relies on dynamic remodeling of energy supply patterns. The Warburg effect describes cancer cells' preferential utilization of glycolysis over oxidative phosphorylation (OXPHOS) for ATP production through glucose fermentation to lactate, even under aerobic conditions with functional mitochondria [13]. Modern studies reveal the Warburg effect arises not from defective mitochondrial respiration as originally proposed [14], but rather serves tumor-specific biological requirements distinct from normal tissue physiology. Unlike normal cells' OXPHOS-dominated homeostasis, tumors develop unique metabolic plasticity through spatiotemporal coordination of Warburg effect and OXPHOS: glycolytic bursts support rapid proliferation, while mitochondrial respiration sustains metastasis and therapy resistance.

Emerging research demonstrates a sophisticated dynamic equilibrium between Warburg metabolism and OXPHOS, transcending simplistic binary opposition. While Kukurugya's metabolic model confirmed glycolysis's kinetic advantage in ATP production [13], glycolytic tumors paradoxically require mitochondrial functions. For instance, Metastasis-Associated Protein 1 (MTA1) enhances OXPHOS via ATP synthase upregulation to drive colorectal liver metastases [15], and prostate cancer cells shift from glycolysis to OXPHOS under high-density conditions [16], challenging the "glycolytic metastasis" dogma.

The classical Warburg paradigm is being redefined, as tumors exhibit metabolic flexibility to adapt their energy strategies according to microenvironmental constraints. Under proliferative or hypoxic stress, tumors activate glycolysis through mechanisms like OMA1-mediated metabolic coordination in colorectal cancer [17], while Skp2 maintains cell cycle-coupled metabolism - Tricarboxylic Acid (TCA) cycle in G1 phase and glycolysis in S phase via IDH1/2 stabilization in prostate cancer [18]. Conversely, glycolytic toxicity (e.g., lactic acidosis) induces OXPHOS revival, creating therapeutic vulnerabilities - tumor sensitivity to OXPHOS inhibitors increases 100-10,000 fold under these conditions [19].

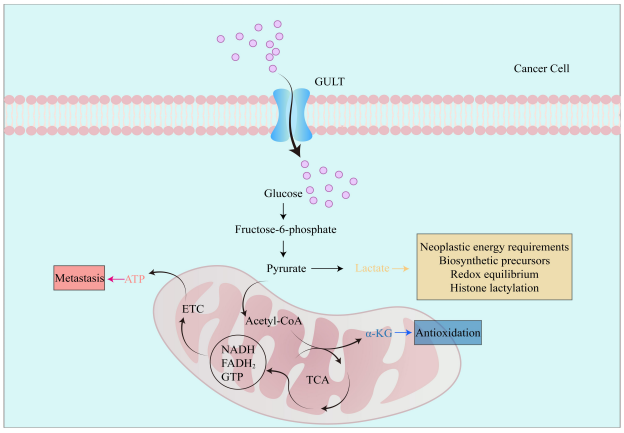

Figure 2. Metabolic-Epigenetic Nexus in Mitochondria of Cancer Cell: Glycolytic Reprogramming, Lactate-Driven Histone Modifications, and Redox Adaptation in Metastatic Progression.

2.2 Regulation of Redox Homeostasis

Under dual pressures of hypermetabolism and hostile microenvironments, cancer cells construct multi-layered redox defense networks through functional expansion of metabolic intermediates. Glutamine metabolism, TCA cycle reprogramming, and glycolytic byproducts form coordinated regulatory axes to combat oxidative stress. Notably, these metabolites not only maintain tumor-intrinsic redox balance but also remodel the microenvironment through epigenetic modifications and immune cell polarization, creating pro-tumorigenic ecological niches. Metabolic regulation of redox homeostasis unveils the profound evolutionary mechanism through which tumors convert survival stress into progression momentum.

In cancers, enhanced dependency on glutamine uptake and catabolism profoundly impacts redox regulation through metabolic reprogramming. Studies reveal glutamine "addiction" in various malignancies - tumor cells critically depend on glutamine as both energy substrate and biosynthetic precursor [20]. PDAC cells utilize an unconventional glutamine pathway: glutamine-derived aspartate undergoes cytosolic transport and GOT1-mediated conversion to oxaloacetate, then malate/pyruvate, elevating NADPH/NADP+ ratio to combat oxidative stress [21]. TCA cycle remodeling demonstrates environmental adaptability - α-ketoglutarate (KG) acts as antioxidant under oxidative stress, reducing Reactive Oxygen Species (ROS) production [22], enabling metabolic equilibrium maintenance in adverse conditions. The Warburg effect further regulates glutamine metabolism and ROS dynamics, enabling persistent redox homeostasis [23].

2.3 Biosynthetic Support

The ultimate objective of metabolic reprogramming is to supply biosynthetic precursors for uncontrolled tumor proliferation. By hijacking glycolytic branches, remodeling TCA cycle flux, and enhancing glutaminolysis, cancer cells redirect metabolic flows toward nucleotide, amino acid, and lipid precursor synthesis. For instance: enhanced glycolysis provides

abundant precursors for nucleotide/amino acid/lipid biosynthesis to sustain rapid division [24]; hypoxic melanoma cells utilize reverse TCA flux to synthesize fatty acids from glutamine, critical for proliferation [25]; glutaminolysis supplies nitrogen for nucleic acid synthesis, with increased glutamine uptake boosting ATP and macromolecule production [26]. PDAC cells employ a non-canonical glutamine pathway where aspartate-malate flux supports biosynthesis [21]. This "metabolic diversion" strategy not only surpasses normal anabolic rate limitations but also exploits non-canonical enzyme functions: glycolytic enzyme HK2 phosphorylates IκBα to activate NF-κB pathway, upregulating PD-L1 and directly mediating immune evasion [27], highlighting the central role of metabolic networks in malignant transformation.

2.4 Lipid Metabolic Reprogramming

Lipids (FAs, cholesterol, phospholipids, lipoproteins) fulfill essential physiological roles in membrane architecture, energy storage, and signal transduction, while playing critical roles in tumorigenesis, progression, and metastasis [28,29]. Lipid metabolic remodeling represents a critical evolutionary adaptation to energy crises and membrane biogenesis demands in malignancies. Upregulation of lipogenic regulators in cancers involves both aberrant de novo lipogenesis and enhanced exogenous lipid uptake. Amplified fatty acid synthesis provides structural membrane components and bioenergetic substrates to fuel rapid proliferation [30-32]. The unique lipid composition of cancer cell membranes is vital for survival, with tumors exhibiting both quantitative lipid accumulation and qualitative compositional changes to meet specialized physiological demands [33]. Alterations in lipid metabolism remodel the entire tumor microenvironment, impairing immune cell function and antitumor responses [34]. Tumor-specific lipid metabolic patterns demonstrate metabolic plasticity breadth while providing rationale for targeting lipogenic enzymes in combination with immunotherapy.

3. Mitochondrial Dynamics and Cancer Invasion

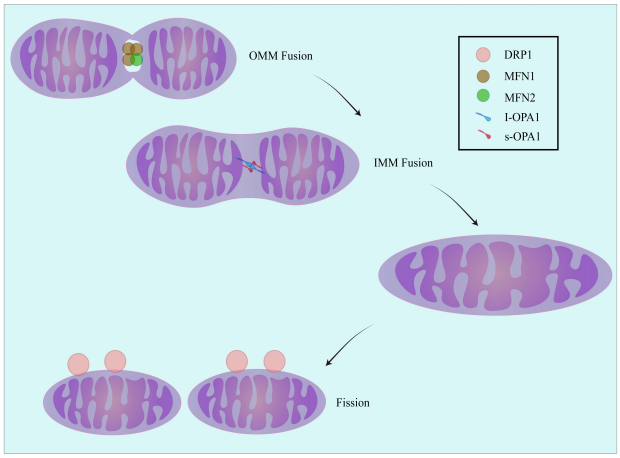

Figure 3. Mitochondrial Fusion and Fission.

Mitochondrial dynamics refers to the homeostatic process maintaining tubular networks through continuous fusion/fission cycles (Figure 3), which orchestrates morphology, size, quantity, and distribution - essential for cellular physiology [35-37]. Perturbations in mitochondrial dynamics disrupt functional integrity, driving pathological progression including carcinogenesis [36], with emerging evidence highlighting its mechanistic link to metastatic dissemination [38,39].

3.1 Mitochondrial Fission-Driven Invasive Phenotypes

Mitochondrial fission, a tightly regulated process mediated by dynamin-related protein 1 (Drp1), governs organellar morphology and quantity while coordinating metabolic signaling and cell fate determination - mechanisms deeply implicated in oncogenesis [40-42]. Drp1-mediated fission promotes tumor progression, as evidenced in esophageal squamous cell carcinoma (ESCC) where Drp1 overexpression activates cGAS-STING-induced autophagy to drive malignancy [43]. Drp1 enhances metastatic competency across malignancies: metastatic breast cancers exhibit elevated Drp1 expression/activity [38]; lung adenocarcinoma migration correlates with Drp1 levels [41]; glioma invasion depends on Drp1-RHOA/ROCK1-mediated cytoskeletal remodeling via filopodia regulation [44]. Functional validation in triple-negative breast cancer (TNBC) shows pharmacogenetic induction of mitochondrial fragmentation paradoxically suppresses metastasis, challenging conventional paradigms [45].

Mitochondrial fragmentation via Drp1 facilitates Warburg metabolism, providing energetic/anabolic support for metastatic dissemination. Paradoxically, mitochondrial fission factor (MFF) amplification diminishes bioenergetic capacity through dual suppression of oxidative and glycolytic metabolism [46]. While fission generally promotes invasion, MFF-driven fragmentation unexpectedly reduces CSC viability, highlighting context-dependent metabolic regulation [46]. Latent brain metastases employ mitochondrial fragmentation to activate FAO, maintaining metabolic flexibility during microenvironmental adaptation [47]. Hepatocellular carcinoma models show fission activation upregulates lipogenesis while suppressing β-oxidation, redirecting glycolytic intermediates to support proliferation [48]. Fission remodels tumor-stroma crosstalk - prostate cancer CAFs engage in metabolic symbiosis with cancer cells [49], while PI3K/Akt/mTOR and MAPK pathways integrate fission signals to drive invasion [45].

3.2 Mitochondrial Fusion Deficits and Metastatic Potential

Mitochondrial fusion requires coordinated outer/inner membrane remodeling: outer membrane GTPases Mitofusins (Mfn1/2) mediate homologous interactions through complex formation [50-52], while inner membrane cristae maintenance involves OPA1 GTPase activity that correlates with OXPHOS efficiency [51,53]. Fusion homeostasis optimizes bioenergetic output, enables inter-mitochondrial mtDNA exchange [54], and

maintains functional integration with cellular physiology. Metastatic outcomes depend on fusion equilibrium - physiological fusion mitigates ROS toxicity [38], whereas excessive fusion triggers bioenergetic overload and mitotic catastrophe [55,56].

3.3 Imbalance of mitochondrial dynamics and cancer development

In summary, enhanced mitochondrial fission critically supports cancer cell proliferation/survival and drives metastasis via metabolic reprogramming, while fusion enhances metabolic adaptability and bioenergetic output to promote therapeutic resistance. Paradoxically, emerging evidence suggests fusion may exert tumor-suppressive effects in specific contexts. PDAC studies demonstrate that mitochondrial fusion restoration rescues cristae architecture, attenuates oxidative metabolism, and confers therapeutic vulnerability [57]. Genetic/pharmacological targeting of OPA1-mediated fusion in TNBC models impairs metastatic competency through bioenergetic crisis induction [58].

While fission and fusion exhibit context-dependent effects on cancer survival, malignant cells dynamically balance these processes to meet evolving metabolic and bioenergetic demands. Although core regulators (e.g., Drp1, Mfns) have been identified, their cancer-type-specific mechanisms and crosstalk with signaling pathways require deeper characterization, as do the metabolic heterogeneity and context-dependent vulnerabilities across malignancies.

4. Mitochondrial Stress Signaling

Mitochondrial stress signaling encompasses molecular cascades initiated under organellar duress, which propagate intracellularly to elicit adaptive responses [59,60]. In oncology, mitochondrial stress signaling has emerged as critical for tumor survival under microenvironmental stresses (hypoxia, nutrient scarcity), driving metabolic rewiring to sustain proliferation (Figure 4) [61-63].

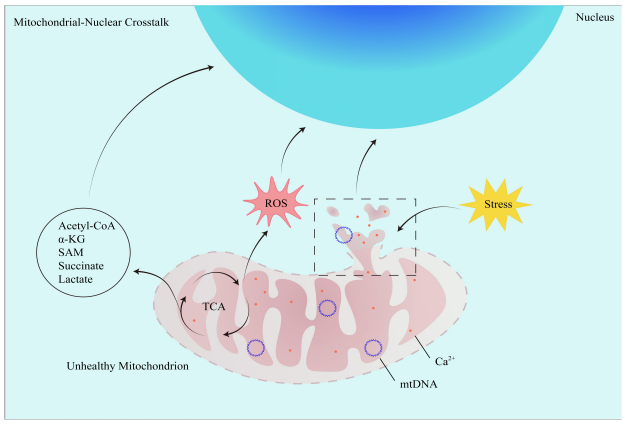

Figure 4. Mitochondrial Dysfunction Orchestrates Nuclear Reprogramming in Cancer Cells.

4.1 The Double-Edged Sword of ROS

Reactive oxygen species (ROS), highly reactive molecules generated through mitochondrial electron transport chain activity, serve as signaling mediators under physiological conditions, dynamically regulating tumor survival, metastasis, and therapy resistance(Figure 1). However, ROS imbalance induces oxidative stress, causing macromolecular damage while paradoxically modulating malignant progression [64-66].

At low concentrations, ROS act as pro-tumorigenic signals through DNA oxidation (e.g., guanine→8-oxodG [67]) and strand breaks. Remarkably, even subtoxic H2O2 levels induce oxidative clustered DNA lesions (OCDLs) and replication-independent DSBs [67]. ROS activate proliferative pathways like Ras-Raf-MEK-ERK cascade [68,69], where sustained ERK1/2 phosphorylation drives G1/S transition through cyclin induction and tumor suppressor silencing [70,71]. Vascular Endothelial Growth Factor (VEGF) plays a central role in tumor angiogenesis [72], which can be upregulated by reactive oxygen species (ROS) through stabilizing and activating hypoxia-inducible factor 1α (HIF-1α) and activating the nuclear factor κB (NF-κB) pathway, while its expression is also induced by MAPK pathway upregulation [73-76]. Additionally, ROS activate EMT-associated transcription factors to induce epithelial-mesenchymal transition in tumor cells, enhancing invasion and metastasis [77,78]. ROS also remodel tumor microenvironments by inducing immune cell apoptosis/functional suppression [79,80] and promoting normal fibroblast transdifferentiation into cancer-associated fibroblasts (CAFs) [81,82], thereby creating a protumorigenic niche.

Supraphysiological ROS activate counter-regulatory pathways like p38 MAPK, inducing G2/M arrest by antagonizing pro-growth ERK signaling [68,83-85]. Excessive ROS activate both intrinsic and extrinsic apoptotic pathways: 1) ROS oxidize mitochondrial membrane components (cardiolipin/VDAC), increasing permeability and cytochrome c release [86-89]; 2) ROS upregulate pro-apoptotic Bax while downregulating anti-apoptotic Bcl-2/Mcl-1, enhancing MOMP [90-92]; 3) Cytochrome c forms apoptosomes with Apaf-1 and procaspase-9, activating caspase-9/-3 cascade [93,94]. In the extrinsic pathway, ROS: 1) Upregulate death receptors (Fas/DR4/DR5) [95]; 2) Enhance FasL-receptor binding [96]; 3) Activate caspase-8 via FADD adaptors, initiating effector caspase cascade [97]. ROS induce ER stress-mediated apoptosis via: 1) Calcium dysregulation through oxidized channels [98,99]; 2) PERK-eIF2α-ATF4 axis activation causing CHOP overexpression [100-102]; 3) Caspase-12 activation initiating executioner caspases [103,104]. Paradoxically, while ROS-induced DNA damage drives mutagenesis, catastrophic genomic lesions ultimately activate apoptotic checkpoints [105].

4.2 Mitochondrial Unfolded Protein Response (UPR^{mt})

UPRmt represents an evolutionarily conserved adaptive mechanism that preserves mitochondrial proteostasis by upregulating chaperones and proteases through stress-responsive transcriptional programs. Proteotoxic stress induces UPRmt-mediated transcriptional adaptation, deploying HSP60/LONP1 complexes to eliminate damaged proteins [106-108]. UPRmt activation initiates adaptive programs facilitating mitochondrial recovery, metabolic plasticity, and innate immune modulation [109]. Cancer cells hijack UPRmt to resolve replication stress-induced proteotoxicity, maintaining mitochondrial fitness during malignant progression [110,111]. The UPRmt maintains mitochondrial proteostasis to support pre-metastatic adaptation, and targeting its critical regulatory nodes could enhance chemotherapeutic sensitivity.

Neoplastic mitochondria endure dual assaults: electron transport chain-derived oxidative damage and replication error-prone mtDNA synthesis. Unchecked mtROS induces proteotoxic collapse, necessitating UPRmt-regulated chaperone-mediated refolding and protease-dependent degradation of damaged proteins [110]. Malignant subpopulations exhibit UPRmt hyperactivation as pre-adaptive strategy, maintaining redox equilibrium to fuel metastatic outgrowth [112]. Mitochondrial proteotoxicity induces: 1) ATF5 nuclear translocation activating UPRmt genes [113]; 2) ROS-mediated DNAJA1 oxidation enhancing HSP70-c-mtProt interaction [114]; 3) HSF1 liberation driving compensatory transcriptional programs [114].

Non-pathological UPRmt induction confers systemic benefits via mitohormetic strengthening of stress response networks [112]. Oncogenic UPRmt reprogramming creates self-reinforcing loops that sustain proliferative and metastatic programs [111]. In prostate cancer, the HSP60-ClpP axis sustains malignancy through c-Myc-driven expression and functional coordination, restoring oncogenic mitochondrial activity [115]. The SIRT3-UPRmt axis drives metastasis, with high UPRmt activity signatures (7-gene panel) predicting poor outcomes in breast cancer patients [112]. UPRmt-upregulated antioxidants (SOD1/2) establish "mitochondrial fitness zones" that neutralize oxidative insults in tumors [116].

5. Mitochondrial-Nuclear Crosstalk

Mitochondria maintain residual genomes but predominantly rely on nuclear-encoded proteins imported from cytosol. This genomic segregation necessitates sophisticated mitochondrial-nuclear communication to preserve cellular functionality and adaptability [117-119]. This inter-organellar dialogue integrates metabolic reprogramming, death signaling, ionic balance, and adaptive survival mechanisms under pathophysiological conditions [120]. Anterograde signaling governs nuclear genes encoding mitochondrial proteins (NGEMPs) expression to sustain mitochondrial functions and metabolic adaptation, mechanisms co-opted by tumors to meet oncogenic demands [121-124]. Our focus herein centers on mitochondrial retrograde regulation of nuclear activity in oncogenic contexts.

5.1 Retrograde Signaling Pathways

Mitochondrial retrograde signaling (MRS) enables organelle-to-nucleus communication via specific molecular messengers, regulating nuclear gene expression to coordinate stress responses, metabolic adaptation, and environmental acclimatization [125,126].

Ca^{2+} serves as pivotal retrograde mediator - physiological mitochondrial uptake occurs via low-affinity transporters requiring microdomain Ca^{2+} gradients [127], while oncogenic dysfunction disrupts Ca^{2+} homeostasis, triggering pro-survival signaling. Mitochondrial dysfunction leads to increased cytosolic calcium concentration and activates calmodulin, which in turn activates multiple downstream effectors such as nuclear factor-κB (NF-κB), nuclear factor-activated T cells (NFAT), and activated transcription factors (ATF). These transcription factors regulate the expression of genes involved in cell proliferation, survival, and metabolism [125,126]. Pharmacological Hsp90 blockade triggers mitochondrial Ca^{2+} efflux, causing ER stress-mediated CHOP upregulation and tumor cell death [128]. Mitochondrial Ca^{2+} dysregulation activates MAPK/NF-κB/mTOR pathways, enhancing proliferation, invasion, and therapy resistance [129-131]. Oncogenic Ca^{2+} signaling reprograms kinase networks (ERK/IKK/mTORC1) to promote metastatic adaptation and chemoresistance [129-131].

Stress-induced nuclear translocation of mitochondrial proteins mediates direct gene regulation: GPS2 coordinates H3K9 demethylation and Pol II activation [132], while ATFS-1 activates mitochondrial stress response genes [133].

Cytosolic mtDNA activates innate immunity through pattern recognition receptors [134], creating immunogenic microenvironments that influence oncologic outcomes [135,136]. mtDNA liberation constitutes conserved stress response, hyperactivated in malignancies through diverse mechanisms [137]. Tumor microenvironment stressors (metabolic shifts, lipid overload) induce ROS-mediated mtDNA damage and mitophagy, facilitating mtDNA escape via mitochondrial-derived vesicles [138-142]. Pathological IMM permeability enables mtDNA pore-mediated release [137,143], while fumarate accumulation drives MDV-dependent mtDNA export [144]. Tumor-derived EVs transfer mtDNA to immune cells, altering their functional states [142]. Liberated mtDNA activates cGAS-STING signaling [145], reprograms nuclear transcription [135], and triggers damage associated molecular patterns (DAMPs)-mediated immunity [146,147], collectively shaping inflammatory landscapes and oncologic trajectories.

5.2 Metabolite-Mediated Chromatin Remodeling

Mitochondrial metabolites translocate to nuclei as substrates/cofactors for chromatin-modifying enzymes, regulating gene expression through DNA methylation

and histone modifications [148,149]. This metabolism-epigenetics crosstalk provides novel insights into oncogenesis and therapeutic development [150].

Normal cells generate acetyl-CoA via mitochondrial TCA cycle, while cancer cells exhibit profound metabolic rewiring [151,152]. These alterations impact both bioenergetics and histone acetylation patterns through spatial-temporal regulation of acetyl-CoA availability [148,153,154]. Cancer-associated metabolic reprogramming enhances fatty acid oxidation [151,155] and upregulates ATP-citRate synthase (ACLY) [156], optimizing acetyl-CoA production/utilization. Mitochondrial acetyl-CoA converts to acetyl-carnitine via carnitine acetyltransferase (CAT), transported to nuclei and reconverted to acetyl-CoA by nuclear CAT, providing histone acetyltransferase (HAT) substrates for histone acetylation [157-159]. At the same time, cancer cells exhibit dysregulated HAT/histone deacetylase (HDAC) equilibrium, causing pathological histone acetylation patterns [160-162]. Acetylation-induced chromatin decompaction facilitates pioneer factor binding and mediates bromodomain-containing protein recruitment, synergistically activating oncogenic transcription [162,163]. Acetylation-mediated chromatin remodeling regulates oncogenes/tumor suppressors [162,164,165], while HDAC inhibitors modulate cell cycle/apoptosis [160,166,167] and metastatic potential [168] through acetylation dynamics.

S-adenosylmethionine (SAM), synthesized via methionine adenosyltransferase (MAT)-mediated methionine/ATP condensation [169], serves as universal methyl donor for DNA/histone methylation and other biosynthetic processes [170]. Mitochondrial defects in cancer impair one-carbon metabolism [171,172] and ATP production, disrupting SAM biosynthesis. SAM depletion induces genome-wide hypomethylation [173,174], whereas SAM supplementation hypermethylates DNA [175], demonstrating dose-dependent epigenetic regulation. Context-specific SAM depletion enables proto-oncogene activation via promoter demethylation, pharmacologically reversible through methyl donor supplementation [173]. Under SAM deficiency, H3K9 monomethylation preserves heterochromatin integrity and enables epigenetic memory restoration upon metabolic recovery [176]. In hepatocellular carcinoma (HCC), MAT1A downregulation and MAT2A upregulation reduce hepatic SAM levels. MAT1A-KO mice exhibit SAM deficiency with macrovesicular steatosis, monocyte infiltration, and HCC development. Colorectal cancer models show SAM depletion correlates with enhanced proliferation, survival, and angiogenesis [177]. SAM deficiency drives tumor progression through integrated metabolic-enzymatic-epigenetic dysregulation of DNA/histone methylation [178-181]. Tumor methylation dynamics significantly correlate with patient survival outcomes [182].

TCA intermediates α-KG and succinate regulate histone demethylation through competitive modulation of KDMs [183,184]. α-KG is an essential cofactor for a variety of α-KG-dependent dioxidases [185,186], and α-KG-dependent histone demethylases, such as KDM4A and JARID1B, are aberrently expressed in a variety of cancers, affecting gene expression and cellular function [187,188]. Succinate antagonizes α-KG by competitively inhibiting KDMs, stabilizing repressive histone marks [184,189]. Metabolic control of α-KG/succinate balance regulates stem cell fate decisions through TET/KDM-mediated DNA/histone demethylation [190,191]. Pharmacological modulation of α-KG/succinate levels enables precise control of chromatin states and stemness-associated transcription.

Lactate serves as metabolic transmitter coordinating: 1) MDSC polarization, 2) T cell exhaustion, 3) deubiquitinase activation in tumor cells. Histone lactylation - lactoyl-lysine PTM - enhances chromatin accessibility and transcriptional activation [191-193]. Tumor lactate overload drives hyperlactylation, correlating with aggressive phenotypes and poor prognosis across malignancies [194-196]. This epigenetic-metabolic circuit links glycolytic flux to PD-L1 upregulation [197] and MCT4 overexpression [198], enforcing therapeutic resistance.

Mitochondrial calcium dysregulation and mtDNA release drive nuclear transcriptional reprogramming and immune evasion. Mitochondrial-nuclear crosstalk, mediated by metabolite-driven epigenetic remodeling and mtDNA-triggered immunomodulation, serves as a central hub for tumor heterogeneity and immune escape. Targeting this interaction network not only suppresses malignant progression but also reprograms the immune microenvironment, offering a novel paradigm for developing "metabolism-epigenetics-immunity" integrated precision therapies.

6. Mitochondrial Crosstalk with the Tumor Microenvironment

As a heterogeneous milieu, the TME integrates immunocytes, cancer-associated fibroblasts, angiogenic networks, and matrix components [199,200] into self-reinforcing circuits that orchestrate malignant progression through biophysical and biochemical interactions [201]. Mitochondrial-TME interactions operate through metabolic reprogramming, immunomodulation, and paracrine signaling - mechanisms that extend beyond bioenergetic support to govern tumor initiation, dissemination, and therapeutic resistance.

6.1 Mitochondrial Regulation of Immune Evasion and Metastatic Competence

Mitochondria regulate immune cell activation, differentiation, and effector functions through metabolic modulation, ROS production, and cell death regulation [202], thereby shaping immune responses and facilitating tumor immune escape. As mentioned, mitochondrial involvement in energy production confers metabolic flexibility to cancer cells, predominantly relying on glycolysis for bioenergetic demands [202,203]. This specific metabolic mode helps tumor cells to escape the host immune response. On the one hand, the decrease of pH in the tumor microenvironment caused by the

production of large amounts of lactic acid by tumor cells inhibits the function of immune effector cells, affects the metabolism of immune cells, and promotes the production of immunosuppressive cells such as Treg cells [204-206], or the nutrient deficiency in the tumor microenvironment caused by massive glucose consumption affects the activation and effector function of T cells [207].On the other hand, mitochondrial dysfunction—particularly metabolic reprogramming-directly impacts the expression of immune checkpoint molecules on tumor cells. This occurs through direct genetic regulation and indirect metabolite-mediated epigenetic modulation of PD-1, PD-L1, and CTLA-4 expression [208,209]. Studies demonstrate that epigenetic loss of the ATP synthase subunit ATP5H triggers core metabolic rewiring, leading to ROS accumulation and stabilization of hypoxia-inducible factor 1α (HIF-1α) under normoxic conditions [210]. HIF-1α stabilization subsequently upregulates PD-L1 expression, thereby suppressing T cell-mediated antitumor activity [211]. Horizontal mtDNA transfer from tumor to TILs induces metabolic paralysis and premature senescence in recipient T cells, compromising antitumor immunity through mitochondrial dysfunction propagation [141]. Mitochondrial reprogramming establishes pre-metastatic niches through TME remodeling, priming distant sites for metastatic colonization [212].

6.2 Intercellular Mitochondrial Transfer in the Tumor Microenvironment

Mitochondria can traffic between cells via intercellular transfer mechanisms [213], a phenomenon particularly prevalent in tumor ecosystems that critically influences malignant progression and immune evasion [214]. Neoplastic networks engage in mitochondrial commerce with diverse TME residents - from bone marrow-derived cells to vascular endothelia - through specialized intercellular conduits [215-217]. Acquired mitochondria reprogram recipient cell bioenergetics [218], epigenetic landscapes [219], and survival signaling [220], collectively remodeling TME physicochemical properties to favor malignancy [221-224].

Therapeutic and microenvironmental stresses (ROS, nutrient deprivation, chemotherapeutics) induce mitochondrial dysfunction that triggers compensatory transfer mechanisms in tumors [225,226]. Breast cancer models demonstrate oxidative stress (H_2O_2 exposure) significantly enhances mitochondrial trafficking between malignant and stromal cells [227]. mtDNA damage-induced respiratory collapse (<30% baseline ATP production) triggers mitochondrial vampirism - tumor cells replenish functional mitochondria from adjacent stroma to regain bioenergetic competence [214]. Implanting defective mitochondria (Mito8344/P-Mito8344) into recipient cells induces metabolic reprogramming - glycolytic flux increases 3-fold while oxygen consumption decreases by 60% [227]. There is mitochondrial transfer between stromal cells, immune cells and cancer cells in the tumor microenvironment. Bone marrow stromal cells can transfer mitochondria to myeloma cells by forming tunneling nanotubes (TNTs) connecting myeloma cells and stromal cells [228], CAFs can allow the exchange of mitochondria and other cargo between cells through contact-dependent tunneling nanotubes (TNTs) with breast cancer cells [229], and nearly unidirectional mitochondria presented by T cells to tumor cells Somatic metastasis causes "enhanced metabolism" of tumor cells and "depletion" of immune cells [221].

Mitochondrial trafficking employs TNTs [228], EVs [230], and fusogenic mechanisms [215], representing novel therapeutic targets to disrupt metabolic symbiosis and restore treatment sensitivity [231].

7. Prospect: Therapeutic Strategies Targeting Mitochondria

Mitochondria function as an "adaptive engine" in tumor evolution, driving carcinogenesis, metastasis, and therapy resistance through metabolic reprogramming, dynamic regulation, stress signaling, and mitochondrial-nuclear crosstalk. These mechanisms position mitochondrial-targeted therapies as pivotal approaches to overcome limitations of conventional treatments. Mitochondrial-targeted therapeutic strategies aim to selectively eliminate cancer cells by disrupting tumor-specific mitochondrial functions while minimizing off-target effects on normal cells. Current mitochondrial-targeted strategies capitalize on tumor-specific metabolic vulnerabilities, inducing oncogenic metabolic crisis and programmed cell death through selective disruption of energy production, genetic stability, or dynamic equilibrium. Compared to traditional chemotherapy's broad cytotoxicity, these strategies enhance selectivity through dual mechanisms: 1) Cancer cells' heightened mitochondrial activity increases susceptibility to inhibition; 2) Targeted delivery systems exploit tumor mitochondrial properties for spatial drug enrichment, reducing off-target toxicity. Therapeutic objectives extend beyond direct tumor killing to disrupting mitochondrial-mediated chemoresistance mechanisms, thereby reversing drug resistance and enhancing combination therapy efficacy. Current research employs multidimensional interventions: metabolic reprogramming control, bioenergetic machinery disruption, genetic system targeting, and smart delivery technologies to overcome drug accumulation barriers, ultimately establishing precision strike systems against tumor mitochondrial adaptation networks.

Due to the Warburg effect, many cancers exhibit high dependence on glycolysis, making glycolysis targeting a promising anticancer strategy. Recent advances in studying glycolytic enzymes/proteins have identified multiple therapeutic targets: glucose transporters (GLUTs) [232], hexokinase (HK) [233,234], phosphofructokinase (PFK) [235], pyruvate kinase M2 (PKM2) [236], lactate dehydrogenase A (LDHA) [237], and pyruvate dehydrogenase kinase (PDK) [238]. Various natural and synthetic compounds effectively inhibit these glycolytic targets, demonstrating antitumor potential. The electron transport chain (ETC) is central to mitochondrial energetics. Many tumors critically depend on ETC function; its inhibition may selectively kill

cancer cells with minimal normal cell toxicity. Examples include complex I inhibitors metformin and IACS-010759 [239,240], and complex III inhibitor atovaquone [241], which suppress ATP production to induce bioenergetic collapse. Similarly, targeting the TCA cycle represents a viable strategy to inhibit tumor growth and proliferation. CPI-613 targets TCA cycle enzymes pyruvate dehydrogenase complex (PDC) and α-ketoglutarate dehydrogenase (KGDH), reducing metabolic flexibility and depleting nutrient reserves in tumors [238,242]. Pyruvate transport inhibitor UK-5099 disrupts TCA cycle by blocking mitochondrial pyruvate uptake [243]. Modulating TCA intermediates like succinate and their downstream signaling pathways represents another potential therapeutic approach [244]. Enhanced fatty acid synthase (FASN) activity in tumors supports membrane biogenesis and energy storage. FASN inhibition effectively suppresses tumor growth/metastasis [245,246], with clinical candidates including GSK2194069, JNJ-54302833, IPI-9119, and TVB-2640 [247]. FAO provides critical energy for tumors. FAO inhibitors etomoxir and perhexiline demonstrate antitumor efficacy [248,249], while trimetazidine targets mitochondrial trifunctional protein (MTP) [250]. mtDNA-targeting agents induce tumor death via mitochondrial dysfunction, ROS overproduction, and apoptosis. Anthracyclines (doxorubicin) [251], cisplatin [252], topoisomerase I inhibitors (homoharringtonine/topotecan) [253], and Pol γ inhibitors (Congo red) [254] all damage mtDNA.

However, traditional chemotherapeutic agents lack targeting specificity, leading to nonspecific distribution in normal tissues and mitochondrial membrane impermeability, which prevents effective drug accumulation at target sites. To address these limitations, mitochondrial-targeted drug delivery systems have been developed to precisely transport therapeutic agents to cancer cell mitochondria. These systems not only enhance therapeutic efficacy but also reduce off-target toxicity, thereby overcoming the drawbacks of conventional chemotherapy. Leveraging the hyperpolarized mitochondrial membrane potential in cancer cells, positively charged carriers such as triphenylphosphonium (TPP)-modified nanoparticles have been engineered [255,256]. Mitochondria-targeting peptide-based nanoplatforms efficiently deliver anticancer drugs to tumor mitochondria, significantly enhancing antitumor activity [257]. Additionally, liposomes and polymeric nanocarriers serve as critical delivery platforms due to their biocompatibility and tunability [258,259]. Mitochondrial-targeted delivery systems markedly improve chemotherapeutic outcomes [256,260] and demonstrate substantial potential in overcoming multidrug resistance [63,261]. Integration with other modalities like photodynamic therapy (PDT), photothermal therapy (PTT), and chemodynamic therapy further amplifies therapeutic efficacy [262,263].

Current targeting strategies can disrupt tumor energy supply, but metabolic plasticity may activate compensatory pathways. Future therapies should combine multiple metabolic nodes (e.g., mitochondrial-targeted agents + traditional chemotherapeutics) to synergistically amplify therapeutic stress. Although current delivery systems improve mitochondrial drug accumulation, challenges remain in addressing tumor heterogeneity-induced targeting variability and mitochondrial membrane potential differences affecting drug enrichment. Mitochondrial-targeted therapy will evolve from broad cytotoxicity to precision regulation, integrating metabolism, genetics, immunology, and engineering to establish "diagnosis-treatment-monitoring" precision medicine frameworks. Advances in AI-driven drug design, single-cell metabolomics, and smart delivery systems may enable real-time intervention in mitochondrial networks, offering revolutionary solutions for drug resistance and metastasis. These advancements will transform cancer treatment and potentially provide novel strategies for metabolic disorders and age-related diseases.

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

All authors have approved the manuscript and agreed to submission.

Availability of Data and Material

Not applicable

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

J. Zhang, J. Xu and B. Hu conceived the work, analyzed the data, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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