The Role of Mitochondrial Signaling Pathways in Tumor Chemoresistance

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Abstract. Chemoresistance is a major obstacle in cancer chemotherapy, with mitochondria playing a central role in its underlying mechanisms. Mitochondria enhance the survival and antioxidant defense capabilities of tumor cells through various pathways, including metabolic reprogramming, fusion/fission dynamics, autophagy, and anti-apoptosis, enabling effective adaptation to chemotherapeutic stress. Based on the pivotal role of mitochondria in tumor chemoresistance, targeting mitochondria has emerged as a novel intervention strategy to enhance chemotherapy efficacy. This review comprehensively summarizes the role of mitochondria in tumor chemoresistance, elucidates its core mechanisms, and explores the potential of mitochondria-targeted therapies.

Keywords: Tumor, Chemoresistance, Mitochondrial Metabolic Reprogramming, Mitochondrial Quality Control, Targeted Therapy.

1. Introduction

Malignant tumors represent a major threat to global health. In 2024, approximately 18.7 million new cancer cases and 9.7 million cancer deaths were reported worldwide [1]. Asia bears nearly half of this burden, with a notably rising incidence among younger populations. Chemotherapy, a systemic treatment utilizing chemical agents to kill or inhibit cancer cells, remains a first-line therapy for various malignancies such as lung, breast, and gastric cancers [2]. This is due to its broad-spectrum anti-tumor activity, well-defined dose-response relationship, and established clinical protocols, despite rapid advancements in targeted therapy and immunotherapy. Chemotherapy also plays multiple critical roles in the comprehensive treatment of solid tumors: preoperative neoadjuvant chemotherapy reduces tumor volume to improve surgical resection rates. In contrast, postoperative adjuvant chemotherapy eliminates micrometastases to reduce recurrence risk. For patients with advanced metastatic disease, chemotherapy effectively controls tumor progression, prolongs survival, and alleviates symptoms (e.g., malignant effusions, pain). However, chemotherapy efficacy is often severely limited by tumor resistance (both intrinsic and acquired), leading to treatment failure and recurrence. Overcoming chemoresistance is thus a key challenge in improving cancer treatment outcomes. Tumor chemoresistance results from synergistic effects of multiple factors, including epigenetic modifications (e.g., RNA methylation), physical barriers in the tumor microenvironment (TME) (e.g., hyaluronic acid (HA) accumulation), mitochondrial metabolic abnormalities (e.g., TRAP1, SDH, SDHB), and activation of stem cell pathways (Wnt/AKT). Recent research has revealed that mitochondria—the central hubs of cellular energy metabolism—play a crucial role in driving chemoresistance in tumor cells. Resistant tumor cells exhibit a high dependence on mitochondrial metabolic reprogramming, particularly enhanced oxidative phosphorylation (OXPHOS), to maintain high energy supply and redox homeostasis. Simultaneously, mitochondria demonstrate significant metabolic flexibility, dynamically regulating the glycolysis/OXPHOS balance to adapt to stressful microenvironments. Furthermore, disruptions in sophisticated mitochondrial quality control—the dynamic equilibrium process involving continuous monitoring, selective clearance of damaged mitochondria (mitophagy), and regulation of mitochondrial fusion/fission—shift towards states favoring chemoresistance development.

Leveraging the pivotal role of mitochondria in resistance, targeting their metabolic pathways or quality control has emerged as a novel intervention strategy to reverse resistance and enhance

chemotherapy efficacy. This review summarizes the role of mitochondria in tumor chemoresistance, dissects its core mechanisms (metabolic reprogramming and quality control), and explores the potential of related targeted therapies.

2. Mechanisms of Mitochondrial Involvement in Tumor Chemoresistance

Mitochondria are responsible for biosynthesis, metabolism, energy generation, signal transduction, and cellular homeostasis in normal cells. They contain proteins essential for cell growth, development, and even the regulation of cell death, playing a crucial role in determining cell fate. The critical role of mitochondria in cancer has been recognized for a long time. As early as the 1930s, Otto Warburg reported that mitochondrial dysfunction contributes to cancer progression [1]. Furthermore, mitochondrial functions vary depending on cancer types, genetic mutations, and environmental stresses. During cancer chemotherapy, mitochondria act as organelles sensing cellular stress and play a key role in the survival and death of cancer cells. Several mechanisms have been proposed to explain its contribution to chemoresistance, including: altered mitochondrial metabolism, activation of anti-apoptotic pathways, mitophagy, mitochondrial quality control, and mitochondrial transfer. As cancer research advances, new mechanisms will continue to be discovered, necessitating further studies to understand their interactions and how to target them to overcome chemoresistance. This review focuses on mitochondrial metabolism, mitochondrial quality control, and the potential for targeted therapies to enhance tumor cell chemosensitivity.

2.1. Mitochondrial Metabolism

Mitochondria are key intracellular organelles, often called the cell's "powerhouses," responsible for energy metabolism and biosynthesis. Mitochondria in normal cells interact relatively minimally with the extracellular environment, primarily maintaining function through intracellular signaling. Normal cells predominantly rely on oxidative phosphorylation (OXPHOS) for energy production, efficiently converting nutrients to ATP via the mitochondrial electron transport chain (ETC). In contrast, tumor cell mitochondria exhibit unique metabolic processes: they interact with the tumor microenvironment (e.g., hypoxia, inflammation, acidic conditions), regulating metabolic pathways and signaling to support tumor progression. For instance, under hypoxia, tumor cells adapt via glycolysis—the "Warburg effect." This metabolic shift, though less efficient, rapidly generates energy to meet the demands of rapid tumor cell proliferation, producing large amounts of lactate.

Recent studies indicate that chemoresistant tumor cells exhibit adaptive mitochondrial metabolic rewiring. Mutations in mitochondrial metabolism lead to increased dependence on OXPHOS to maintain a higher ATP level, which significantly boosts energy supply beyond that of normal cells to support energy-intensive tumor growth. This metabolic shift renders traditional chemotherapeutic agents insufficient to effectively contain tumor cell growth [3, 4, 6]. Chen et al demonstrated in an MDA-MB-231 triple-negative breast cancer model that shikonin reversed resistance to traditional chemotherapeutics (e.g., doxorubicin) by inhibiting PGC-1α-mediated mitochondrial biogenesis (reducing ATP production by 67%) [6]. Guo et al developed aterpyridine platinum(II) complex(TTP) that selectively inhibits thioredoxin reductase (TrxR) in lung cancer A549 cells, disrupting the SDHB-overexpression-activated succinate-HIF-1α resistance pathway and increasing mitochondrial ROS levels by 3.2-fold [7]. In chemoresistant ovarian cancer OVCAR-3 cells, Qi et al identified the VDAC1-GRP75-IP3R complex-mediated calcium homeostasis as critical for maintaining ATP5F1A-dependent OXPHOS and GLS1-driven glutamine metabolism, a mechanism increasing paclitaxel resistance by 3.5-fold [8]. These breakthroughs not only confirm the mitochondrial metabolic network as a core hub in chemoresistance but also provide precise molecular blueprints for developing combination therapies targeting mitochondrial metabolic nodes.

2.2. Mitochondrial Quality Control

Mitochondria have evolved a complex quality control system to maintain functional stability, including mitochondrial-derived vesicles (MDVs), mitochondrial fusion/fission, and mitophagy [9]. Dysregulation of these mechanisms in tumor cells is a core factor mediating chemoresistance. The following section focuses on mitochondrial fusion and fission. Mitochondria are highly dynamic organelles, constantly undergoing fusion and fission as part of "mitochondrial dynamics." Fusion and fission correlate with the extent and duration of mitochondrial damage: severe/prolonged damage favors fission, while mild/transient stress favors fusion [10].

2.2.1 Mitochondrial Fusion

Mitochondrial fusion is the merging of two or more mitochondria, involving mitofusins (MFN1/2)-mediated outer membrane fusion and optic atrophy 1 (OPA1)-mediated inner membrane fusion. As key components of mitochondrial dynamics, the dynamic interplay between fusion and fission maintains mitochondrial homeostasis. This fusion-fission balance (mitochondrial dynamics) plays a critical role in chemoresistance. Fusion enhances tumor cell resistance by repairing damaged mitochondria, a process mediated by proteins like MFN1/2 and OPA1 [10]. Fused mitochondrial networks confer survival advantages to resistant tumor cells through four key mechanisms, closely linked to MFN2-mediated network remodeling:

(1) Energy Metabolic Remodeling

The fusion of mitochondria forms an interconnected network that enhances the cooperative efficiency of the electron transport chain (ETC). Tanaka et al showed that UQCRC2-dependent Complex III activity increased by 58% in fused SK-MEL-28 melanoma cells, sustaining high ATP levels (>3.5 μmol/mg protein) [11]. Fumarate inhibits PINK1-Parkin pathway-mediated clearance of fused mitochondria by succinylating Parkin at Cys323/451 [12].

(2) Enhanced Antioxidant Defense

MFN2 directly regulates SOD2 activity, increasing the GSH/GSSG ratio from 2.1 to 3.8 in doxorubicin-resistant MCF-7 cells [10]. Chandel et al demonstrated that MFN2 overexpression in A549 lung cancer cells maintains mitochondrial membrane potential ($\Delta\Psi m > -120mV$), effectively clearing chemotherapy-induced ROS (reduced by 67%) [13].

(3) Resistance to Apoptotic Signaling

OPA1-mediated cristae stability inhibits Bax/Bak oligomerization. Chan et al showed that caspase-3 activity in OPA1-overexpressing SKOV3 cells after paclitaxel treatment was only 33% of controls ($P<0.001$) [14].

(4) Mitophagy Escape

Intact networks evade PINK1/Parkin recognition via steric hindrance. Kimmelman et al found that MFN1 knockout in PANC-1 cells increased the mitophagy marker LC3-II/LC3-I ratio from 0.5 to 1.9 [15].

2.2.2 Mitochondrial Fission

Mitochondrial fission is a highly regulated process where a mitochondrion divides into two or more daughter mitochondria. Core proteins involved in mitochondrial fission include dynamin-related protein 1 (Drp1), mitochondrial fission factor (Mff), and mitochondrial fission protein 1 (FIS1). Drp1-mediated mitochondrial fission plays a dual role in tumor metabolic adaptation and the immune microenvironment [16]. Fission increases mitochondrial surface area, enhancing OXPHOS efficiency, particularly by driving the shift from glycolysis to OXPHOS during energy stress. Drp1-mediated cristae remodeling promotes respiratory chain complex assembly and suppresses glycolysis via SIRT1-NAD+ signaling. Scorrano et al confirmed that metformin combined with Drp1 siRNA in MCF-7 breast cancer cells inhibited the SIRT1-NAD+ pathway, reducing OXPHOS efficiency by 58% and blocking the glycolysis-OXPHOS switch [17]. This process also impacts tumor immune response: Drp1-dependent fission enhances macrophage phagocytosis via WIP/WASP phase separation. For example, Drp1 agonist Dynasore increased fission in B16F10 melanoma cells, boosting macrophage phagocytosis by 2.7-fold via WIP/WASP phase separation [18]. In resistance cells, fission exhibits

context-dependence. Cassidy et al found that ROS in hypoxic microenvironments promotes fission in A2780 cells by inhibiting Drp1 Ser637 phosphorylation, leading to cisplatin resistance (IC50 increased 3.2-fold). The Drp1 inhibitor Mdivi-1 restored phosphorylation levels and reversed resistance [19].

3. Targeting Mitochondria to Enhance Tumor Chemosensitivity

Mitochondria, as central organelles in cellular energy metabolism and apoptosis regulation, are closely associated with tumor drug resistance. Mitochondria-targeting strategies can reverse chemoresistance through precise intervention in metabolic pathways, oxidative stress, mitophagy, and mitochondrial dynamics. The following summarizes key mechanisms and representative studies: To disrupt mitochondrial metabolic pathways, various agents have been developed to target metabolic reprogramming—a major contributor to chemoresistance. For instance, phenformin alters mitochondrial ultrastructure and inhibits mtDNA-related protein expression, thereby suppressing oxidative phosphorylation (OXPHOS) and sensitizing triple-negative breast cancer to doxorubicin [20]. Similarly, a mitochondrial-targeted microneedle system co-loaded with DOX-TPP and ZIF-67 nanoparticles has been designed to utilize the tumor microenvironment for enhanced mitochondrial accumulation, effectively inducing dual apoptosis-ferroptosis and markedly improving therapeutic response in resistant models [21]. Another approach capitalizes on the inherent metabolic vulnerability of leukemia cells to simultaneous OXPHOS uncoupling (via CCCP) and glycolysis inhibition (via 2-DG), resulting in catastrophic ATP depletion and cell death [22].

In terms of modulating mitochondrial oxidative stress, targeting the redox balance provides another effective route. The small molecule BTD-001 reduces OXPHOS efficiency by interfering with mtDNA transcription, thereby synergizing with gemcitabine in pancreatic cancer [23]. Meanwhile, the micropeptide MRPIP—derived from a long non-coding RNA—disrupts mitochondrial RNA processing by binding to HSD17B10, leading to OXPHOS collapse and ROS accumulation under nutrient stress, which significantly enhances sorafenib efficacy in hepatocellular carcinoma [24].

First-line chemotherapeutic agents such as cisplatin, paclitaxel, doxorubicin, and gemcitabine not only induce tumor cell apoptosis through mechanisms like DNA damage, microtubule stabilization, or oxidative stress but also sequentially activate signaling pathways such as HIF-1α/BNIP3, TRPML3-lysosome-Ca^{2+}, or Notch. This leads to the upregulation of key mitophagy-related proteins, including PINK1, Parkin, and LC3-II, which selectively remove damaged mitochondria, reduce the release of ROS and apoptotic factors, and maintain ATP homeostasis, thereby enabling tumor cells to evade death signals and develop significant tolerance. Since this autophagic protective mechanism can be further amplified by hypoxic conditions or signaling pathways such as TRPML3 and Notch, combining autophagy inhibitors, HIF-1α inhibitors, or WSGC peptides to disrupt this process can prevent the effective clearance of cisplatin-induced damage. As a result, the threshold for drug resistance is lowered, and drug sensitivity is markedly restored. This demonstrates that these chemotherapeutic agents rely on the fine-tuned regulation of mitophagy to achieve "self-rescue," and targeted intervention of this pathway can reverse their drug resistance.[25-27]

Finally, targeting mitochondrial dynamics—such as fission and fusion—has proven valuable. The Drp1 inhibitor Mdivi-1 restores cisplatin sensitivity in ovarian cancer by preventing excessive fission [27]. In contrast, ABT-737 promotes Drp1/Fis1-mediated mitochondrial fragmentation in cisplatin-resistant cells, leading to amplified cytochrome C release and apoptosis, illustrating a context-dependent role of fission in chemosensitivity [28]. TMQ0153, a tetrahydrobenzimidazole derivative, is a key compound for enhancing chemosensitivity in acute myeloid leukemia (AML) by targeting mitochondrial dynamics. It disrupts mitochondrial morphology and function in AML cells by inhibiting the mitochondrial fusion protein OPA1 and reducing MFN2 levels. Specifically, TMQ0153 induces reactive oxygen species (ROS) generation, suppresses oxidative phosphorylation (OXPHOS), and causes mitochondrial membrane potential (MMP) depolarization, thereby triggering

caspase-dependent apoptosis. Furthermore, it drives metabolic reprogramming by shifting cellular energy production from mitochondrial respiration to glycolysis, which collectively impairs AML cell survival. In vivo, TMQ0153 alone significantly reduces tumor volume and weight in MV4-11 xenograft models.

Moreover, TMQ0153 demonstrates synergistic effects in combination therapies. When combined with gilteritinib, a FLT3 inhibitor, the dual approach simultaneously targets mitochondrial dynamics and aberrant FLT3 signaling in FLT3-mutated AML models (e.g., MV4-11 and MOLM-14-luc cells). This combination reduces leukemic burden and prolongs survival in NSG mice. In a triple regimen with venetoclax (a BCL2 inhibitor) and azacitidine, TMQ0153 enhances therapeutic efficacy against TP53-mutated AML (U937-luc cells) through inhibition of mitochondrial Complex II and depletion of glutathione (GSH), leading to improved survival outcomes in mice. These findings underscore the potential of TMQ0153 as a promising therapeutic strategy for drug-resistant AML.[29]

4. Conclusion

The central role of mitochondria in chemoresistance reveals the survival ingenuity tumor cells exhibit when facing energy crises. From "powerhouses" to "resistance engines," the multifaceted nature of mitochondria provides a new strategic fulcrum in the fight against cancer. Future research must delve deeper into the spatiotemporal complexity of its molecular networks, advancing targeting strategies from "single-axis blockade" to "multi-axis synergy." Only by unveiling the complete regulatory landscape of mitochondrial involvement in resistance can we overcome current therapeutic bottlenecks, ultimately transforming the tumor cell's "shield of survival" into a precisely targetable "Achilles' heel," igniting hope for conquering the century-old challenge of chemoresistance.

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