Review



# Mitochondrial Dynamics in the Metabolic Reprogramming and Cellular Signaling: Implications for Cancer Progression and Therapy Resistance

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Posted Date: 8 May 2026

doi: 10.20944/preprints202605.0521.v1

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 doi:10.20944/preprints202605.0521.v1



*Review*

# Mitochondrial Dynamics in the Metabolic Reprogramming and Cellular Signaling: Implications for Cancer Progression and Therapy Resistance

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**Abstract**

Mitochondria play essential roles in cellular metabolism and signaling, regulating biosynthetic pathways, calcium homeostasis, redox balance, and cell fate beyond ATP production. Their continual remodeling through fusion, fission, and mitophagy maintains mitochondrial quality control and adapts organelle function to cellular demands. Here, we review how mitochondrial dynamics, fusion, fission, and mitophagy modulate metabolic reprogramming and signaling to drive cancer progression and therapy resistance. Emerging evidence indicates that in cancer, mitochondrial fusion enhances respiratory efficiency and oxidative phosphorylation, whereas fission promotes glycolytic adaptation, rapid biomass accumulation, and stress tolerance. Mitophagy further refines metabolic fitness by eliminating damaged mitochondria and sustaining redox homeostasis. Together, these processes underscore that dysregulation of mitochondrial dynamics is a hallmark of cancer and a key driver of metabolic reprogramming and therapeutic resistance. In this review, we summarize how mitochondrial fusion, fission, and mitophagy govern metabolic circuitry in cancer development and therapy resistance. We highlight their functional impact on tumor progression and discuss emerging therapeutic strategies targeting mitochondrial dynamics and associated machinery. Understanding this dynamic metabolic crosstalk may reveal new vulnerabilities and guide the development of mitochondria-targeted cancer therapies.

**Keywords:** mitochondrial dynamics; mitochondrial fission; mitochondrial fusion; mitophagy; mitochondrial metabolism; oxidative phosphorylation (oxphos); tca cycle; reactive oxygen species (ros); mitochondrial dna (mtDNA); mitochondrial dysfunction; bioenergetics; cancer; cell death; cell survival; drug resistance; immune evasion; mitochondria-targeted therapy

## 1. Introduction

Mitochondria are widely recognized as the powerhouses of the cell because they generate the primary cellular energy currency, adenosine triphosphate (ATP). Beyond energy production, mitochondria regulate numerous cellular processes, including key metabolic pathways such as the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), as well as a few reactions in nucleotide and lipid biosynthesis, redox homeostasis, calcium signaling, apoptosis, and cell survival [1–6]. Through these interconnected metabolic networks, mitochondria integrate nutrient availability with cellular energy demands and environmental stresses such as hypoxia, nutrient deprivation, and anoikis [7–10]. In response to these challenges, cells activate adaptive metabolic programs, including glutaminolysis, fatty acid oxidation (FAO), serine-glycine metabolism, and aspartate synthesis, to sustain survival and proliferation [11–19]. Cancer cells frequently exploit these adaptive pathways when exposed to nutrient limitation or metabolic stress, a phenomenon known as metabolic reprogramming. One of the earliest descriptions of altered metabolism in cancer was reported by Otto Warburg in the early 20th century. The Warburg effect describes the preference of

 doi:10.20944/preprints202605.0521.v1



cancer cells to utilize glycolysis for energy production even in the presence of sufficient oxygen, a process termed aerobic glycolysis [20]. Initially, this observation led to the assumption that mitochondrial function was impaired in cancer cells [21]. A recent study further supports the idea that cancer cells with an impaired pyruvate import complex exhibit defective pyruvate utilization in the TCA cycle, leading to metabolic reprogramming toward glycolysis [22].

However, mitochondria continue to play central roles in cancer cell metabolism by coordinating multiple biosynthetic and bioenergetic pathways under both normal and stress conditions. For example, mitochondrial metabolism is maintained through anaplerotic reactions that replenish TCA cycle intermediates. Glutamine can be converted to glutamate and subsequently to $\alpha$-ketoglutarate, thereby refilling the TCA cycle and supporting mitochondrial metabolism [23–25]. Similarly, cytosolic pyruvate can enter mitochondria and be converted to oxaloacetate by mitochondrial pyruvate carboxylase (PC), thereby feeding into the TCA cycle and sustaining metabolic flux [26,27].

Although the Warburg effect historically dominated the understanding of cancer metabolism, it is now clear that tumor metabolism extends far beyond this paradigm. Many cancers retain functional mitochondria and actively rely on mitochondrial oxidative metabolism, glutaminolysis, fatty acid oxidation, and one-carbon metabolism to support rapid proliferation, metastatic progression, cancer stemness, immune evasion, and resistance to therapy, driven by aberrant mitochondrial signaling and dynamics [28–31].

Accumulating evidence indicates that proteins controlling mitochondrial dynamics are frequently dysregulated in cancer, where they contribute to tumor progression, metastasis, and therapy resistance. In particular, mitochondrial fission factors such as dynamin-related protein 1 (DRP1) are often overexpressed and have been implicated in cancer initiation and progression [32]. Changes in mitochondrial morphology directly affect substrate utilization, reactive oxygen species (ROS) production, mitochondrial DNA stability, mitophagy, and apoptotic sensitivity, thereby actively reshaping cellular metabolism to meet the demands of rapidly proliferating tumor cells. However, the precise mechanistic links between mitochondrial structural remodeling and metabolic rewiring remain incompletely defined and warrant further investigation.

In this review, we summarize the current understanding of how mitochondrial dynamics regulate cancer cell metabolism and metabolic reprogramming. We discuss the molecular machinery governing mitochondrial fusion and fission and examine how these processes influence cancer cell proliferation, metastasis, immune evasion, and therapeutic resistance. Finally, we highlight emerging pharmacological strategies targeting mitochondrial dynamics, with particular emphasis on their potential applications in cancer therapy. A deeper understanding of the interplay between mitochondrial structure, metabolism, and signaling may reveal novel vulnerabilities that can be exploited for therapeutic intervention in cancer.

## 2. Overview of Mitochondrial Dynamics

Mitochondria undergo continuous structural remodeling through fusion, fission, mitophagy, and network reorganization, a process collectively termed mitochondrial dynamics. These dynamic actions are essential for preserving mitochondrial integrity, ensuring bioenergetic efficiency, supporting metabolic flexibility, and enabling cell survival and growth. By integrating metabolic cues, stress signals, and developmental inputs, mitochondrial dynamics shape critical cellular processes, including cell survival, apoptosis, and metabolic adaptation, thereby positioning mitochondria as central coordinators of cellular homeostasis and stress responses [33].

### *2.1. Mitochondrial Fusion*

Mitochondrial fusion occurs by mixing mitochondrial contents, including mitochondrial DNA (mtDNA), proteins, lipids, and metabolites, thereby sustaining mitochondrial function and enabling adaptation to stress, such as metabolic and oxidative stress. Mechanistically, fusion occurs in two coordinated steps that involve the merging of the outer and inner mitochondrial membranes. Outer membrane fusion is mediated by the large GTPases Mitofusin 1 (MFN1) and Mitofusin 2 (MFN2),

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which form homotypic or heterotypic dimers of MFN1 and MFN2 between two different mitochondria to tether and merge their outer membranes [34].

Next, inner membrane fusion is regulated by Optic Atrophy 1 (OPA1), a dynamin-related GTPase localized to the inner mitochondrial membrane (Figure 1A) [35]. OPA1 not only mediates fusion of the inner membrane but also governs cristae architecture, thereby influencing the organization of the respiratory chain and controlling cytochrome c sequestration within the cristae during physiological conditions. Under pro-apoptotic stimuli, OPA1-dependent cristae remodeling modulates the accessibility of cytochrome c and facilitates its release, thereby shaping the amplitude and timing of apoptosis.

Mitochondrial fusion is functionally associated with increased OXPHOS, enhanced mitochondrial membrane potential, efficient ATP production, and resistance to cellular stress [36,37]. Fused mitochondria often support anabolic metabolism and are observed in cells with great energy demand [36].

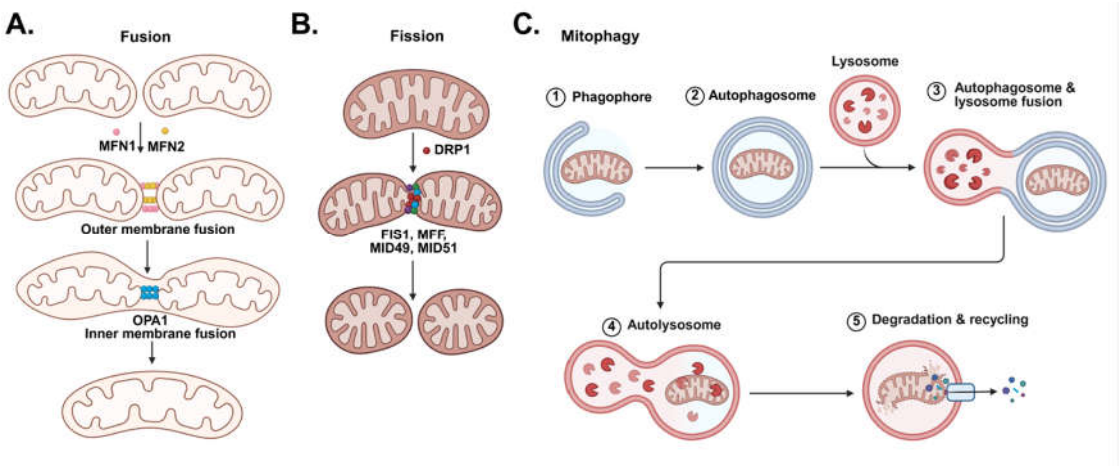


**Figure 1.** Mitochondrial dynamics: fission, fusion, and mitophagy. (**A**) Mitochondrial fusion occurs through the coordinated action of mitofusins (MFN1 and MFN2), which regulate outer mitochondrial membrane fusion, whereas OPA1 mediates inner mitochondrial membrane fusion. (**B**) Mitochondrial fission is primarily regulated by DRP1 (DNM1L). Adaptor proteins, including MFF, FIS1, MID49, and MID51, recruit and facilitate DRP1 assembly on the mitochondrial surface, leading to mitochondrial fragmentation. (**C**) Mitophagy is the selective degradation of damaged mitochondria via autophagy. Damaged mitochondria are sequestered into autophagosomes, which subsequently fuse with lysosomes to form autolysosomes, where mitochondrial components are degraded.

### *2.2. Mitochondrial Fission*

In contrast, mitochondrial fission generates smaller, discrete mitochondria and is essential for mitochondrial distribution during cell division, quality control, and mitophagy. Increased mitochondrial fragmentation is frequently associated with elevated ROS production, increased glycolytic metabolism, activation of mitophagy, and apoptotic priming [38].

Mitochondrial fission occurs through the binding of activated DRP1, a cytosolic GTPase, to the adaptor proteins such as Fission1 (FIS1), Mitochondrial Fission Factor (MFF), Mitochondrial dynamics protein 49 (MID49), and Mitochondrial dynamics protein 51 (MID51) on the outer mitochondrial membrane. After DRP1 binds to these adaptor proteins, it oligomerizes and constricts the membrane to drive scission (Figure 1B) [39–42]. It has been reported that DRP1 undergoes various post-translational modifications, including phosphorylation by different kinases, SUMOylation, ubiquitination, and acetylation, which fine-tune its activity in response to metabolic and stress signals [43–47].

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*2.3. Mitophagy*

Mitochondrial fusion and fission are dynamic processes that play essential roles in maintaining cellular energy homeostasis. The coordinated balance between these opposing events regulates mitochondrial morphology, distribution, and functional capacity [45]. Disruption of this equilibrium can lead to mitochondrial dysfunction, altered metabolic activity, and compromised cellular homeostasis, with the accumulation of damaged or dysfunctional mitochondria further perturbing energy balance and metabolic integrity [48].

To preserve mitochondrial quality and functionality, cells employ mitophagy, a specialized form of selective autophagy that targets damaged or superfluous mitochondria for degradation. In this process, defective organelles are selectively recognized and sequestered by the phagophore, an isolation membrane that progressively engulfs the mitochondrion to form a double-membrane autophagosome. The autophagosome subsequently fuses with lysosomes, forming an autophagolysosome, where lysosomal hydrolases degrade mitochondrial proteins, lipids, and nucleic acids [49,50]. The resulting metabolites are recycled back into the cytosol to support cellular metabolism, thereby reinforcing mitochondrial quality control and contributing to metabolic adaptation (Figure 1C).

*2.4. Regulation by Cellular Signals*

Mitochondrial dynamics are regulated by nutrient availability, hypoxia, oncogenic cues, calcium flux, and energy-sensing pathways such as AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) [51–55]. Beyond structural remodeling, these signals are transduced through changes in mitochondrial fusion and fission to reprogram cellular metabolism, survival, and stress adaptation. For example, energy-sensing pathways converge on mitochondrial dynamics, with AMPK activation often promoting fission and mitophagy under low-energy conditions, while mTOR favors fusion and anabolic growth [51,56–58]. Transcriptional coactivators like Peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$/$\beta$ (PGC1$\alpha$/PGC1$\beta$) control the expression of MFN1, MFN2, and other mitochondrial genes, thereby linking growth and oncogenic signaling, such as Yes-associated protein (YAP)/Hippo-related pathways, to mitochondrial fusion and oxidative metabolism [59]. Phosphatase and Tensin Homolog (PTEN)-induced kinase 1 (PINK1) and Parkin (PRKN) orchestrate mitophagy, which in turn shapes ROS signaling, inflammasome activation, and apoptosis, and is itself regulated by oncogenic and stress-response pathways [60]. FIS1, MFF, and Mitochondrial Rho (MIRO) family members act as receptors that couple fission and mitophagy to calcium and kinase signaling, integrating organelle remodeling with cell survival decisions [61].

Taken together, mitochondrial fusion-regulated genes, fission-regulated genes, PGC1$\alpha$/$\beta$, AMPK, and mTOR form a gene network by which mitochondrial dynamics transduce nutrients, stress, and oncogenic signals into metabolic rewiring, ROS signaling, and cell-fate outcomes. Thus, mitochondrial dynamics act as a central signaling hub, linking extracellular and intracellular stress cues to metabolic control, cell-fate decisions, and survival pathways.

## 3. Mitochondrial Dynamics Regulate the Cancer Cell Metabolism

Mitochondrial dynamics are increasingly recognized not only as structural remodeling processes but also as active regulators of metabolic reprogramming in cancer. The balance between fission and fusion defines mitochondrial architecture, cristae organization, substrate utilization, and respiratory efficiency. Through these mechanisms, mitochondrial dynamics directly influence metabolic pathway selection, biosynthetic capacity, redox balance, and tumor cell adaptability. In this section, we will discuss how mitochondrial dynamics modulate metabolic reprogramming and cellular signaling transduction, and highlight mitochondrial dynamics in various metabolic pathways required for cancer cell survival and proliferation.

 doi:10.20944/preprints202605.0521.v1



*3.1. OXPHOS and Glycolysis*

Mitochondrial fusion is generally associated with enhanced OXPHOS. Elongated mitochondria exhibit improved cristae organization, optimized assembly of the electron transport chain (ETC) super complexes, and higher membrane potential, collectively promoting efficient ATP production. Machinery proteins such as MFN1, MFN2, and OPA-1 are linked to regulating OXPHOS in different cancer models. In several cancer models, fused mitochondrial networks support high OXPHOS activity, which is required for metastatic dissemination, therapy resistance, and cancer stem cell maintenance. For example, interleukin-6 (IL-6) upregulates MFN1 expression, which, in turn, promotes OXPHOS and thereby facilitates chemoresistance in acute myeloid leukemia (AML) [62]. In another study, microRNA-126 (miR-126) promotes OXPHOS by stabilizing B-cell lymphoma 2 (BCL-2) through the Sprouty-related, EVH1 domain-containing protein 1 (SPRED1)/extracellular signal-regulated kinase axis, which in turn promotes phosphorylation of MFN1/2 to induce mitofusion and suppress mitofission by regulating DRP1 phosphorylation [63]. Proteasome activator 28γ (PA28γ) is a member of the 20S proteosome complex that regulates the OXPHOS by binding and stabilizing the complement 1q binding protein (C1QBP), which regulates the MFN1/2 and OPA1 expression [64]. OPA1 is another piece of machinery in mitofusion, and its role in maintaining cristae integrity is particularly critical for respiratory capacity. The studies suggest that OPA1 is overexpressed in AML, suppresses ROS production, enhances metabolic reprogramming by increasing OXPHOS, and suppresses apoptosis [65]. E3 ligases play an important role in regulating mitochondrial dynamics. Membrane Associated Ring-CH-Type Finger 5 (MARCH5) is an E3 ligase that degrades OPA1 in cancer cells. Proliferating cell nuclear antigen (PCNA) is highly overexpressed in AML and binds to OPA1, inhibiting MARCH5 binding to OPA1 and promoting mitofusion and OXPHOS [66]. Presenilin-associated rhomboid-like protein (PARL), which is an inner-mitochondrial-membrane rhomboid protease, supports fusion-competent and elongated mitochondria via OPA1 processing, thereby supporting efficient electron transport and OXPHOS [67] (Figure 2A).

In contrast, mitochondrial fission is often associated with a metabolic shift toward glycolysis. DRP1-mediated fragmentation reduces respiratory efficiency and promotes metabolic rewiring toward aerobic glycolysis, facilitating rapid ATP production and biomass synthesis needed for proliferation. Additionally, mitochondrial fission can be triggered under nutrient deprivation. Glutamine deprivation conditions induce ROS-mediated activation of the Mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway, leading to further phosphorylation of DRP1 at Serine 616, increased glycolysis, unaltered OXPHOS, and the promotion of cancer stem cell formation [68].

Fragmented mitochondria are commonly observed in highly proliferative tumors and under oncogenic signaling [69,70]. Mechanistically, DRP1 binding is increased by FIS1 rather than MFF, promoting mitophagy, mitochondrial respiratory cristae (MRC) dynamics, OXPHOS, and ATP production [70]. C-Myc is another important oncogene that plays a key role in rewiring cancer cell metabolism [19]. In a study using hepatoblastoma models, it was shown that C-Myc promotes glycolysis by upregulating DRP1, which increases mitofission; this enhanced mitofission increases the glycolytic phenotype in cells and suppresses MFN1 expression by increasing miR-373-3p, which leads to reduced mitofusion [69]. Some aggressive tumors, such as gliomas and ovarian tumors, exhibit high fission alongside preserved mitochondrial metabolism, underscoring that mitochondrial fragmentation can enhance metabolic plasticity rather than suppress respiration [70,71]. In another study, ETS Proto-Oncogene 1 (ETS1), a transcription factor, directly binds to the DRP1 promoter and increases its expression, leading to increased mitofission and enhanced glycolysis rather than OXPHOS [66]. Overlapping Activity With M-AAA Protease (OMA1) is a stress-activated protease that cleaves long-form OPA1 into short isoforms, which inhibits inner-membrane fusion and promotes mitochondrial fragmentation. This stress-induced fragmentation and reduced fusion correlate with and can promote a metabolic shift toward glycolysis, helping cells cope with energetic or oxidative stress [72]. This glycolytic bias supports nucleotide, amino acid, and lipid biosynthesis by diverting glycolytic intermediates into anabolic pathways. Thus, mitochondrial morphology acts

 doi:10.20944/preprints202605.0521.v1



as a rheostat that balances OXPHOS-dependent energy production with glycolysis-driven biomass production (Figure 2A).

In summary, mitochondrial fusion improves respiratory efficiency and OXPHOS, while fission supports glycolytic adaptation, rapid biomass accumulation, and stress tolerance. Nevertheless, this relationship is context-dependent. Mitofusion not only regulates the OXPHOS but also regulates glucose metabolism. Recent studies suggest that the specificity protein 1 (Sp1) regulates mitochondrial dynamics through MFN1/2, OPA1, and DRP1, and promotes glycolysis [73]. Mitochondrial Fission Process 1 (MTFP1), which participates in the classical fission machinery, serves as a regulator of inner-membrane integrity to promote a glutamine-driven OXPHOS axis [74]. Therefore, this fusion-fission-driven metabolic reprogramming appears to be context-dependent and may allow cancer cells to adapt to different stimuli.

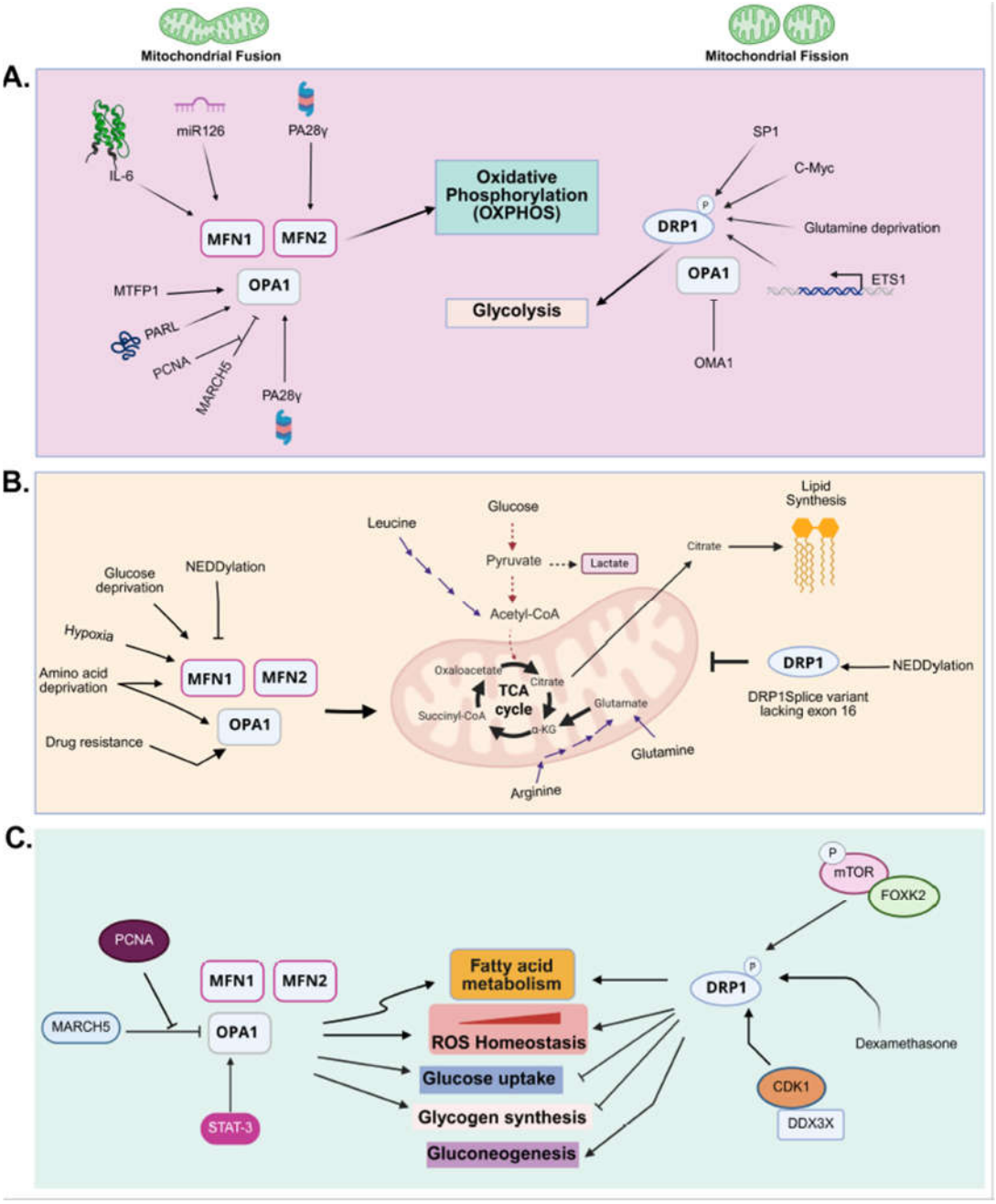


**Figure 2.** Role of mitochondrial dynamics in cancer cell metabolism. (**A**) Mitochondrial dynamics, including fusion and fission, play a central role in regulating cellular metabolism. Mitochondrial fusion is generally associated with enhanced oxidative phosphorylation (OXPHOS), whereas fission is often linked to increased

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glycolytic activity. (**B**) Mitochondrial dynamics influence the tricarboxylic acid (TCA) cycle and anaplerosis by replenishing metabolic intermediates, particularly under conditions of energy, metabolic stress or drug resistance. (**C**) Mitochondrial dynamics regulate multiple metabolic pathways, including fatty acid metabolism, reactive oxygen species (ROS) homeostasis, glycogen synthesis, glucose uptake, and gluconeogenesis.

### *3.2. TCA Cycle and Anaplerosis*

Beyond OXPHOS and glycolysis, mitochondrial dynamics also influence TCA cycle flux and anaplerotic pathways that replenish metabolic intermediates. Fused mitochondria tend to support robust TCA cycling, sustaining citrate production for export into the cytosol. Cytosolic citrate serves as a precursor for lipid synthesis and histone acetylation, linking mitochondrial morphology to epigenetic and biosynthetic programs [75]. Mitochondrial dynamics also regulate glutamine import and metabolism, a major anaplerotic input in cancer cells. Glutamine-derived $\alpha$-ketoglutarate fuels the TCA cycle and supports nucleotide and lipid biosynthesis [29]. Under amino acid starvation conditions, cells increase the hyperfusion through MFN1 and OPA1. Supplementation with glutamine, leucine, and arginine further increases hyperfusion, and knockdown of genes regulating glutaminolysis, the TCA cycle, and purine biosynthesis indicates that hyperfusion is involved in these pathways [76]. Under hypoxia or energy stress, cancer cells frequently utilize reductive carboxylation of glutamine-derived $\alpha$-ketoglutarate to generate citrate for lipid production [77].

Emerging evidence suggests that fragmented mitochondria may favor this metabolic adaptation by reshaping nicotinamide adenine dinucleotide (NAD+/NADH) balance and reorganizing metabolic enzyme localization [78]. Post-translational modifications such as NEDDylation, in which Neural precursor cell expressed, developmentally down-regulated 8 (NEDD8) is conjugated to target proteins, regulate protein stability; inhibition of NEDDylation stabilizes MFN1 and blocks the translocation of the fission protein DRP1, thereby promoting mitochondrial fusion while inhibiting the TCA cycle [79].

Drug-resistant and residual cancer cells often increase the TCA cycle and reprogram metabolic pathways through OPA1-mediated hyperfusion [80]. Further, the DRP1 splice variants were shown to regulate mitofusion. DRP1 splice variant lacking exon 16, has defects in the fission events and promotes the fusion events, enhances the TCA cycle metabolites, and increases the metastasis [81–83]. Through these mechanisms, mitochondrial dynamics regulate the flexibility of TCA cycle engagement and biosynthetic output (Figure 2B).

### *3.3. Fatty Acid Metabolism*

Fatty acid catabolism occurs in the mitochondria to generate energy for the cell. Fused mitochondrial networks are often associated with enhanced fatty acid oxidation (FAO), as elongated mitochondria exhibit improved respiratory coupling and sustained oxidative capacity [84]. FAO provides ATP and NADH/flavin adenine dinucleotide (FADH2) to support tumor survival under nutrient limitation, anchorage-independent growth, and therapeutic resistance [84]. Cluster of Differentiation 96 (CD96) is highly overexpressed in various cancers and enhances mitochondrial FAO via the CD155-CD96-Src-Signal Transducer and Activator of Transcription 3 (Stat3)-Opa1 pathway in breast cancer models [85]. OPA1 has also been shown to increase fatty acid oxidation (FAO) in Acute Myeloid Leukemia. PCNA binds to OPA1 and prevents its interaction with the E3 ubiquitin ligase MARCH5, thereby protecting OPA1 from MARCH5-mediated degradation [66]. In addition, mitochondrial dynamics regulate interactions between mitochondria and lipid droplets. Physical contact sites between these organelles facilitate fatty acid trafficking for either β-oxidation or lipid storage [86]. In metastatic breast cancer cells, elevated lipid content promotes FAO. This metabolic adaptation is regulated by DRP1-mediated mitochondrial fission. Phosphorylation of DRP1 by cyclin-dependent kinase 1 (CDK1) stimulates mitochondrial fission, a process that is coordinated by the DEAD-box helicase 3 (DDX3) [86]. In another study, DRP1 was shown to regulate FAO by interacting with mTOR. Mechanistically, Forkhead box protein K2 (FOXK2) increases mTOR phosphorylation and interacts with both mTOR and DRP1, thereby promoting lipid metabolic

 doi:10.20944/preprints202605.0521.v1



reprogramming [87]. In certain cancers, fragmented mitochondria localize near lipid droplets, promoting rapid lipid mobilization to meet biosynthetic demands. Conversely, fusion can enhance sustained FAO-dependent survival programs. Taken together, mitochondrial dynamics govern not only OXPHOS but also lipid utilization strategies by increasing mitochondrial dynamics and substrate accessibility, thereby contributing to tumor aggressiveness and metabolic resilience (Figure 2C).

### *3.4. Redox Homeostasis and ROS Signaling*

Mitochondrial dynamics play an important role in maintaining cellular redox balance and regulating ROS signaling. Changes in mitochondrial morphology can significantly influence how ROS are produced and managed within the cell. Mitochondrial fission is often associated with elevated ROS levels, largely due to reduced efficiency of the electron transport chain (ETC) and increased electron leakage. Although excessive ROS can damage cellular components and trigger cell death, cancer cells frequently activate survival signaling pathways and antioxidant defense systems to prevent ROS-induced toxicity [88,89]. In contrast, mitochondrial fusion generally supports more efficient electron transport and helps limit excessive ROS generation. However, low or moderate levels of ROS can function as signaling molecules rather than purely damaging agents. In cancer cells, these signaling ROS can activate oncogenic pathways and transcriptional programs that promote OXPHOS, angiogenesis, and metastatic progression [64,90]. ROS also influence several metabolic regulators and transcription factors, including AMPK, Nuclear factor erythroid 2-related factor 2 (NRF2), MYC, and p53, thereby linking mitochondrial structure with broader metabolic control [91–93]. Importantly, oxidative stress can directly activate DRP1, thereby enhancing mitochondrial fission. This creates a positive feedback loop in which mitochondrial fragmentation further increases ROS production. Conversely, mitochondrial fusion can mitigate oxidative stress by improving ETC function and enabling functional complementation across mitochondria, thereby helping maintain redox stability. While ROS generated by fragmentation may support tumor-promoting signaling under controlled conditions, excessive ROS can overwhelm cellular defenses and lead to cell death. Therefore, the balance between mitochondrial fission and fusion plays a critical role in determining the cellular consequences of ROS signaling (Figure 2C).

### *3.5. Other Metabolic Pathways*

It has been reported that mitochondrial dynamics regulate additional metabolic pathways beyond classical energy metabolism, including glycogen metabolism, gluconeogenesis, and de novo purine synthesis. In cells with DRP1 knockdown, enhanced mitochondrial fusion is observed [29,63]. For example, inhibition of mitochondrial fission by suppressing DRP1 activates glycogen synthesis, supporting cell survival in colon cancer [94]. This suggests that loss of DRP1 promotes mitochondrial fusion, which in turn facilitates glucose uptake and glycogen biosynthesis [94]. Similarly, glucocorticoids, such as dexamethasone, induce DRP1 expression, favoring mitochondrial fission and promoting gluconeogenesis [95]. In the context of amino acid availability, amino acid deprivation triggers mitochondrial hyperfusion, mediated by MFN1 and OPA1, whereas supplementation with glutamine, leucine, or arginine further enhances this hyperfused state [76]. Overall, these studies highlight that mitochondrial morphology dynamically coordinates multiple biosynthetic pathways, linking structural plasticity with metabolic adaptation in cancer cells (Figure 2C).

## 4. Mitochondrial Dynamics and Cancer Cell Phenotypes

Mitochondrial dynamics influence several cancer cell phenotypes. Fission driven by increased DRP1 activity fragments mitochondria, reducing OXPHOS while enhancing glycolysis (Warburg effect), which may promote cancer cell proliferation and invasion [96]. Fusion, mediated by elevated MFN1/2 or OPA1 levels, produces elongated mitochondria that increase OXPHOS, driving differentiation and cell survival [96]. However, mitochondrial dynamics can regulate cancer

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phenotypes through mechanisms beyond metabolic reprogramming, including effects on cell-cycle progression, apoptosis resistance, ROS signaling, mitophagy, and DNA-damage responses.

A conserved set of dynamin-related GTPases, including DRP1, MFN1, MFN2, and OPA1, governs mitochondrial morphology. These proteins were initially characterized as structural regulators of mitochondrial networks but are now recognized as key modulators of intracellular signaling and apoptotic sensitivity. For example, increased DRP1-dependent fission has been linked to proliferation and tumor formation, while DRP1 inhibition or MFN1/2 overexpression can reduce growth and trigger apoptosis in cancer cells [97–99]. We also analyzed increased expression of these mitochondrial dynamics proteins such as DRP1 (DNM1L), MFN2 and OPA1, using the GEPIA [100] and TIMER [101–103] databases across various cancers compared with normal patient samples (Figure 3), indicating that fission and fusion-regulated proteins serve as regulators of signaling pathways and affect tumor growth and stress adaptation directly.

This section will discuss how mitochondrial dynamics regulate cancer phenotypes through metabolic reprogramming and fission/fusion-mediated signaling, extending beyond metabolism to control cell-cycle progression, apoptosis resistance, ROS signaling, and mitophagy.

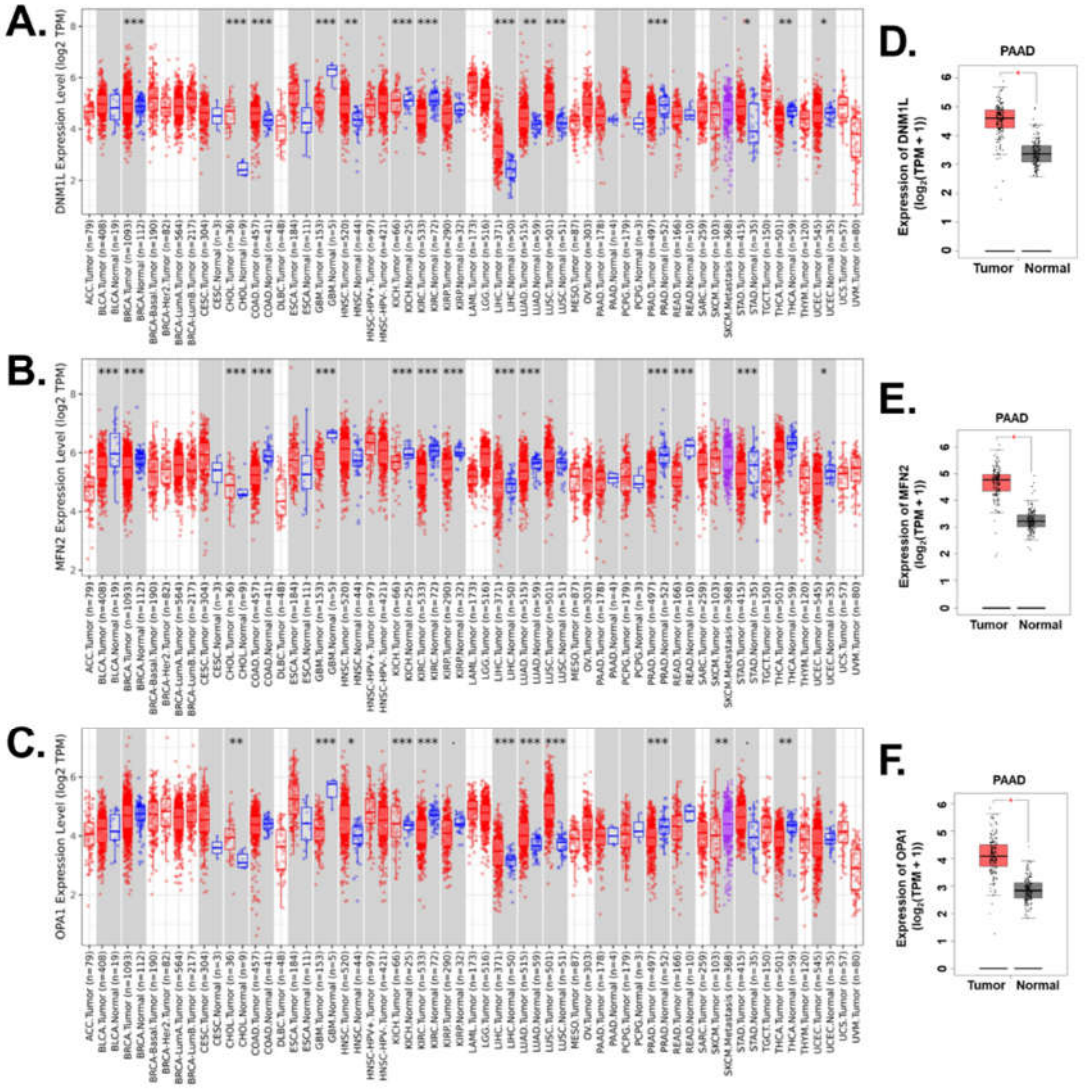


**Figure 3.** Expression profile of mitochondrial dynamics machinery across cancers. (**A**) Expression profile of DRP1 (DNM1L) across multiple cancer types (data retrieved from TIMER datasets). (**B**) Expression profile of MFN2 across multiple cancer types (TIMER datasets). (**C**) Expression profile of OPA1 across multiple cancer types (TIMER datasets). (**D–F**) Expression levels of DRP1, MFN2, and OPA1 in pancreatic adenocarcinoma

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(PAAD), a highly aggressive malignancy characterized by extensive metabolic reprogramming and dysregulation of mitochondrial dynamics.

*4.1. Proliferation and Tumor Growth*

Metabolic reprogramming can also regulate tumor growth and cell proliferation through mitochondrial dynamics. The mitochondrial protein FUN14 domain-containing protein 2 (FUNDC2) is highly overexpressed in various cancers and promotes mitochondrial fragmentation, leading to metabolic reprogramming [104]. The transcription factor SP1, which is highly upregulated in various cancers, has also been linked to mitochondrial remodeling. SP1 regulates the balance between mitochondrial fusion and fission by modulating MFN1/2, OPA1, and DRP1. This shift promotes aerobic glycolysis, enhances cancer cell growth, and inhibits apoptosis [73]. Proteasome activator 28γ (PA28γ) is another regulator that colocalizes with complement 1q binding protein (C1QBP) in mitochondria, promoting mitochondrial fusion, enhancing OXPHOS, and contributing to oral squamous cell carcinoma (OSCC) progression [64]. OPA1, a mitochondrial inner membrane protein, plays a critical role in cell proliferation by regulating mitochondrial fusion and respiration [105]. In another study, OPA1 was shown to be regulated by T-cell immunoglobulin and mucin domain-containing molecule 4 (TIM-4), which promotes OXPHOS. Mechanistically, TIM-4 interacts with annexin A2 (ANXA2) and activates the phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKT) pathway, thereby increasing tumor growth [106].

Mitochondrial dynamics support cancer cell proliferation beyond metabolic reprogramming. For instance, elevated activity of DRP1 has been reported in several malignancies, including hepatocellular carcinoma (HCC) [107], breast cancer [108], and glioblastoma [109], where it correlates with enhanced tumor growth and poor prognosis. Activation of DRP1 is tightly regulated by post-translational modifications, particularly phosphorylation by cell-cycle kinases such as Cyclin-dependent kinase 1 (CDK1) and cyclin B during the G2/M transition [110]. Proteasome non-ATPase regulatory subunit 14 (PSMD14), a deubiquitinating enzyme, regulates DRP1 activity. Increased levels of PSMD14 have been observed in bladder cancer, where it promotes cell growth through DRP1-mediated mitochondrial fission [111]. Another regulator, the E3 ubiquitin ligase Mulan1 (MUL1), suppresses cervical cancer growth. Mechanistically, MUL1 promotes the ubiquitination of FUN14 domain-containing 1 (FUNDC1), an activator of DRP1 [112]. Exosomes act as important carriers of oncogenic proteins and contribute to cancer progression. For example, exosomal 4EBP1 derived from the serum of head and neck cancer (HNC) patients promotes cell proliferation and migration. Mechanistically, exosomal 4EBP1 enhances cancer progression by regulating DRP1 and FIS1 [113]. In some contexts, DRP1 can also function in transcriptional regulation. For example, DRP1 regulates Forkhead box protein M1 (FOXM1) activity, a transcription factor for Matrix metalloproteinase-12 (MMP12), thereby contributing to proliferation and metastasis in HNC [114]. Components of the electron transport chain are also associated with mitochondrial dynamics. NADH: ubiquinone oxidoreductase subunit AB1 (NDUFAB1) is highly overexpressed in HCC and promotes mitochondrial fusion by upregulating MFN1/2 and OPA1 while downregulating DRP1. This shift activates mitophagy and supports cancer progression [115].

Mitophagy represents an adaptive mechanism that enables cancer cell survival under metabolic stress and hypoxic conditions. A recent study showed that hypoxia induces Hypoxia-inducible factor 1-alpha (HIF1α) mediated upregulation of Glycerophosphocholine Phosphodiesterase 1 (GPCPD1), which undergoes depalmitoylation by Lysophospholipase 1 (LYPLA1). Depalmitoylated GPCPD1 translocates to mitochondria, where it binds to Voltage-Dependent Anion Channel 1 (VDAC1) and promotes PRKN interaction, thereby inducing mitophagy. This process enhances cellular adaptation to hypoxia and promotes cell survival [116].

Collectively, mitochondrial dynamics are regulated by multiple cellular signaling pathways, thereby modulating metabolic reprogramming and transcription, leading to cancer cell proliferation and survival (Figure 4).

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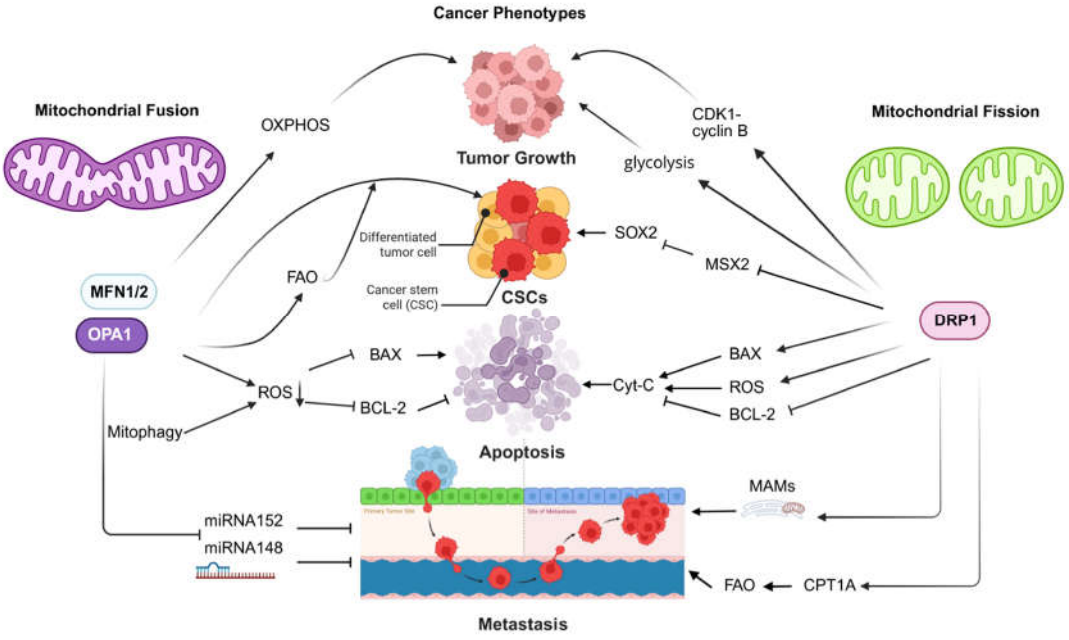


**Figure 4.** Mitochondrial dynamics in the regulation of cancer cell phenotypes. Mitochondrial fusion (**left**) and fission (**right**) contribute to the regulation of multiple cancer-associated phenotypes, including tumor growth, cancer stemness, apoptosis, and anoikis resistance during metastasis.

*4.2. Stemness and Cellular Plasticity*

Cancer cells often acquire resistance to anticancer therapies, and mitochondrial dynamics play a key role in drug resistance, stemness, and cellular plasticity. In one study, the mitochondrial Complement component 1 Q subcomponent-binding protein (C1QBP) was shown to promote cisplatin resistance by upregulating OPA1, thereby increasing mitochondrial fusion and cancer stemness [117]. In some cases, drug treatment itself can enrich cancer stem cell (CSC) populations. For example, cisplatin treatment has been reported to increase CSC levels. Mechanistically, cisplatin induces clusterin expression, which activates AKT-mediated DRP1 phosphorylation, leading to mitochondrial fission. This process promotes mitophagy-mediated degradation of Msh homeobox 2 (MSX2), a SOX2-driven stemness suppressor, thereby maintaining cancer stemness [118]. Cisplatin treatment can also induce the emergence of mesenchymal stem-like cells, which exhibit increased FAO as an adaptive mechanism. Mechanistically, natriuretic peptide receptor A (NPRA), which is upregulated in these cells, stabilizes MFN2, thereby enhancing FAO and stemness [84]. In addition to FAO, lipogenesis also plays an essential role in maintaining cancer stemness by regulating mitochondrial dynamics through mitochondrial dynamics-related proteins [119]. Metastatic breast cancer cells display distinct metabolic phenotypes that support stemness and survival. A recent study demonstrated that increased lipid accumulation enhances FAO and mitochondrial fission. Mechanistically, elevated DDX3 expression promotes FAO and DRP1-mediated mitochondrial fission, thereby enhancing CSC properties [86]. Nutrient deprivation can also promote cancer stemness by modulating mitochondrial dynamics. For instance, glutamine deprivation has been shown to induce CSC properties and chemoresistance through DRP1-mediated mitochondrial fragmentation [68]. In another study, OSCC stem cells exhibited increased DRP1 expression, leading to enhanced mitochondrial fragmentation and reduced fusion. Suppression of DRP1 led to mitochondrial elongation and promoted glutaminolysis by converting $\alpha$-ketoglutarate to glutamate. This metabolic shift induced demethylation of histone H3K27me3, ultimately reducing CSC properties [29]. Mitochondrial fusion proteins have also been implicated in stemness regulation. For example, MFN1 has been shown to promote CSC characteristics in ovarian cancer cells. Ovarian cancer stem cells (OCSC) exhibit increased MFN1 expression, which enhances OXPHOS and supports

 doi:10.20944/preprints202605.0521.v1



stemness [120]. Recent evidence further indicates that acetylated Krueppel-Like Factor 5 (KLF5) suppresses Lactamase Beta (LACTB) expression, thereby promoting colorectal cancer (CRC) stemness and inhibiting differentiation by modulating mitochondrial dynamics via the OMA1/OPA1 axis [121]. Overall, CSCs appear to upregulate mitochondrial dynamics-related proteins as an adaptive mechanism to sustain stemness, metabolic flexibility, and therapy resistance across various cancer types (Figure 4) [85,122].

Drug treatment and nutrient deprivation can reshape mitochondrial dynamics, helping cancer cells maintain stemness and resist therapy. In these contexts, cisplatin, glutamine deprivation, and related stressors often promote DRP1-dependent mitochondrial fission, which supports mitophagy, metabolic adaptation, and survival of cancer stem-like cells. By contrast, some resistance states instead favor mitochondrial fusion through proteins such as OPA1 or MFN1/MFN2, which can enhance oxidative phosphorylation to sustain stemness in specific cancers.

### *4.3. EMT, Invasion, and Metastasis*

Metastasis is a multistep process involving local invasion and epithelial-mesenchymal transition (EMT), intravasation into blood/lymphatic vessels, survival in circulation as circulating tumor cells (CTCs), extravasation into distant organs, and colonization to form secondary tumors. During circulation, cancer cells experience detachment-induced stress known as anoikis. To survive under these conditions, cancer cells develop adaptive mechanisms that confer resistance to anoikis. Mitochondrial dynamics play an important role in regulating metastasis at these different stages. For example, during anoikis resistance, DRP1 interacts with the Binding immunoglobulin Protein (BIP), leading to increased formation of mitochondria-associated endoplasmic reticulum membranes (MAMs), which help maintain mitochondrial dynamics. Mechanistically, AMPK regulates the activation of the MFF-DRP1 axis, promoting DRP1 localization to MAMs [123]. In ovarian cancer, metastasis has been linked to proinflammatory cytokines such as interleukin-6 (IL-6), which promote DRP1-mediated mitochondrial fission. Mechanistically, IL-6 activates ERK1/2 signaling, which, in turn, activates DRP1 and contributes to metastatic progression [124]. Mitochondria-localized proteins also contribute to metastatic regulation. For instance, mitochondrial-localized isoforms of angiotensin II AT2 receptor-interacting proteins (ATIPs) have been shown to promote metastasis by regulating mitochondrial dynamics [125]. In addition, post-translational modifications such as SUMOylation have been reported to regulate mitochondrial dynamics and cancer cell metastasis [126]. As noted earlier, metastatic cancer cells often exhibit distinct metabolic phenotypes that support migration and invasion. FAO is frequently elevated in metastatic cells and is regulated, in part, by mitochondrial dynamics. Mechanistically, interferon regulatory factor 2 binding protein 2 (IRF2BP2) is upregulated in metastatic cells and promotes DRP1 activation. Activated DRP1, in turn, enhances Carnitine Palmitoyltransferase 1A (CPT1A) activity, which is required for FAO, thereby promoting metastasis [127]. Similarly, brain-metastasized breast cancer cells exhibit increased DRP1-mediated FAO [128]. Exosomes also play an important role in cancer cell migration. For example, exosomal 4EBP1 promotes TGF-β expression, which is essential for cell migration, while inhibition of tumor suppressor PTEN [113]. Oncogenic proteins such as the Particularly Interesting New Cysteine-Histidine-Rich protein 1 (PINCH1), a focal adhesion-associated protein, also contribute to cell migration. PINCH1 has been shown to regulate DRP1 activation, promoting mitochondrial fission and enhancing cell migration in head and neck squamous cell carcinoma (HNSC) [129]. In esophageal squamous cell carcinoma (ESCC), DRP1 promotes EMT through the PGC1-α-Nrf1/2 signaling axis, further supporting the role of mitochondrial dynamics in EMT regulation [130]. Mitochondrial fusion protein OPA1 has also been implicated in cancer cell migration. In breast cancer, OPA1 promotes migration by downregulating miRNAs of the 148/152 family, which normally act as inhibitors of tumor growth and migration [131]. In conclusion, mitochondrial dynamics regulate metastasis across its multistep cascade, from EMT/invasion, intravasation, anokis-resistant CTC survival, extravasation, and colonization (Figure 4).

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*4.4. Apoptosis and Cell Survival*

Mitochondria are central regulators of cell fate, determining whether a cell survives or undergoes apoptosis depending on the cellular context. Mitochondrial dynamics proteins play a critical role in maintaining this balance. In general, mitochondrial fusion supports OXPHOS and reduces ROS production, thereby promoting cell survival. In contrast, under conditions such as metabolic stress or anticancer drug treatment, increased mitochondrial fission is often associated with elevated ROS production and induction of apoptosis. For example, mitochondrial proteins such as B-cell lymphoma 2 (Bcl-2)-associated X protein (BAX) directly interact with DRP1, leading to their co-localization on mitochondria. This interaction promotes cytochrome c release and initiates apoptosis in cancer cells under drug treatment conditions [132] (Figure 4). In another study, tumor necrosis factor-$\alpha$-induced protein 8-like-3 (TIPE3), a regulator of the balance between cell survival and cell death, was shown to bind Phosphoglycerate Mutase Family Member 5 (PGAM5). PGAM5 subsequently interacts with BAX and components of the ETC, while reducing DRP1-Serine 637 phosphorylation. This results in increased mitochondrial fission and membrane permeabilization, cytochrome c release, and induction of apoptosis [133]. Peroxiredoxin 1 (PRDX1), an oncogenic protein, suppresses apoptosis by promoting BCL-2 expression and inhibiting BAX activation. Knockdown of PRDX1 enhances apoptosis by increasing BAX activity and caspase activation. Furthermore, PRDX1 depletion induces mitochondrial fragmentation mediated by DRP1, FIS1, and Dynamin 2 (DYN2) [134]. Additional evidence shows that proteins such as Reticulon 4 (RTN4) and Cytoskeleton-Linking Membrane Protein of 63 kDa (CLIMP-63) regulate the recruitment of BAX to the endoplasmic reticulum and mitochondrial membranes, facilitating cytochrome c release and apoptosis through mitochondrial fission [135]. Mitophagy also contributes to apoptosis regulation. PTEN-induced kinase 1 (PINK1)-mediated mitophagy can suppress apoptosis by reducing ROS levels. Conversely, PINK1 depletion or inhibition leads to Translocase of Outer Mitochondrial Membrane 20 (TOM20) oligomerization and recruitment of BAX to the mitochondrial membrane, promoting cytochrome c release and apoptosis [136].

Mitochondrial dynamics have also been implicated in modulating tumor suppressor pathways, including p53/Drp1-mediated mitochondrial fission, to induce apoptosis [137]. The AKT signaling pathway, a key regulator of cell survival, has been shown to inhibit apoptosis. Recent evidence indicates that mitochondrial dynamics proteins, such as DRP1, are regulated by oncogenic AKT signaling. One study shows that inhibition of AKT-mediated phosphorylation of Forkhead box O3a (FOXO3a) by Regorafenib (REGO), a synthetic oral multi-kinase inhibitor with potent antitumor activity, increases FOXO3a nuclear localization, promotes BCL-2-interacting mediator of cell death (BIM) expression, and activates Bax to recruit Drp1 to mitochondria, leading to mitochondrial fission and apoptosis [138] (Figure 4). Mitochondrial dynamics also support cell survival during energy stress. For instance, glioblastoma cells, which are highly dependent on glutamine, respond to glutamine deprivation by upregulating cyclophilin B (CypB), an adaptor protein for CD147. Interaction between CypB and CD147 activates AKT signaling and induces HIF1$\alpha$ and DRP1 activation, leading to increased expression of Glucose Transporter Type 1 (GLUT1), mitochondrial fission, and enhanced cell survival [139].

The anti-apoptotic protein BCL-2 plays a key role in inhibiting apoptosis. Proteins such as BCL2-interacting protein 3 (BNIP3) can suppress BCL-2, leading to cytochrome c release. This is accompanied by increased DRP1-mediated ROS production and reduced MFN1 expression, resulting in decreased OXPHOS and enhanced apoptotic signaling [140] (Figure 4). Remodeling of mitochondrial cristae structure, primarily regulated by OPA1, is a critical determinant of apoptotic sensitivity. It has been shown that OPA1 inhibition induces cytochrome c release and restores sensitivity to anti-Bcl-2 therapy [141]. Collectively, mitochondrial dynamics enable cancer cells to finely balance survival and death signaling pathways, thereby contributing to tumor persistence and resistance to therapy.

Beyond apoptosis, mitochondrial dynamics have also been implicated in other forms of programmed cell death, including gasdermin (GSDME)-mediated pyroptosis and ferroptosis in

 doi:10.20944/preprints202605.0521.v1



various cancer models. For instance, cisplatin, transported by Cytochrome C Oxidase Assembly Homolog 17 (COX17) into cochlear mitochondria, binds Myosin IIA, upregulating DRP1 phosphorylation at Serine 616 and downregulating fusion proteins Mfn1, Mfn2, and OPA1 to promote mitochondrial fission. This shift toward fission increases mitochondrial ROS release, driving pyroptosis and cisplatin-induced cytotoxicity in cochlear hair cells [142]. Praja Ring Finger Ubiquitin Ligase (PJA1) promotes docetaxel resistance in nasopharyngeal carcinoma by ubiquitinating PGAM5 for degradation, thereby enhancing DRP1 phosphorylation at Serine 637 and reducing mitochondrial ROS production. This alteration suppresses mitochondrial dysfunction and GSDME-mediated pyroptosis, thereby inhibiting the anti-tumor immune response [143]. Ruxolitinib (Ruxo) inhibits Janus Kinase 1/2 (JAK1/2)-STAT3 signaling in anaplastic thyroid carcinoma (ATC) cells, repressing DRP1 transactivation and causing mitochondrial fission deficiency. This disruption of mitochondrial dynamics blocks GSDME-mediated pyroptosis [144]. Rosmarinic acid (RA) disrupts mitochondrial dynamics in TNBC cells by significantly upregulating DRP1, thereby promoting mitochondrial fission and leading to mitochondrial dysfunction. This fission, coupled with decreased mitochondrial membrane potential, contributes to RA-induced apoptosis and the inhibition of Triple-Negative Breast Cancer (TNBC) cell proliferation [145].

In summary, mitochondrial dynamics have emerged as central regulators of cancer cell phenotypes, including proliferation, stemness, metastasis, and apoptosis. Continued investigation into the molecular mechanisms linking mitochondrial remodeling with oncogenic signaling will be essential to establish their clinical relevance and potential as effective therapeutic targets.

## 5. Mitochondrial Dynamics in Therapy Resistance

Dysregulation of mitochondrial dynamics, particularly the balance between mitochondrial fusion and fission, plays a critical role in cancer progression and therapeutic resistance. Alterations in these processes disrupt cellular energy homeostasis and promote metabolic reprogramming, including enhanced OXPHOS, glycolysis, and other metabolic pathways. These metabolic adaptations enable tumor cells to suppress apoptosis, maintain survival under stress conditions, and facilitate metastatic progression. Increasing evidence also indicates that mitochondrial dynamics influence the tumor immune microenvironment and contribute to resistance to both conventional chemotherapy and emerging immunotherapies [146].

### *5.1. Fusion-Mediated Therapy Resistance*

Accumulating evidence suggests that enhanced mitochondrial fusion can promote tumor cell survival and contribute to therapy resistance in several cancer types. Mitochondrial fusion, driven by MFN1, MFN2, and OPA1, promotes therapy resistance across multiple cancers by preserving mitochondrial integrity, inhibiting cytochrome c release and apoptosis, and reducing ROS/lipid peroxidation. For example, in tamoxifen-resistant breast cancer cells, MFN1 expression has been shown to increase. Mechanistically, MFN1 interacts with the cristae organizer OPA1, preventing the release of cytochrome c from mitochondria and thereby inhibiting apoptosis. In addition, MFN1 can interact with the pro-apoptotic protein BCL2 Antagonist/Killer 1 (BAK) and inhibit its oligomerization, further blocking apoptotic signaling and promoting resistance to tamoxifen [147]. Inflammatory signaling pathways may also regulate mitochondrial fusion during therapy resistance. In AML, the pro-inflammatory cytokine IL-6 has been shown to increase MFN1 expression, thereby enhancing mitochondrial fusion and promoting chemoresistance [62]. Similarly, treatment with cisplatin in ovarian cancer has been reported to increase the expression levels of VDAC1 and MFN1. These observations suggest that mitochondrial fusion may be associated with cisplatin resistance, although the precise molecular mechanisms linking VDAC1-mediated mitochondrial regulation and chemoresistance require further investigation [148]. OPA1 has also been implicated in cisplatin resistance in non-small cell lung cancer (NSCLC). Mechanistically, the mitochondrial protein C1QBP1 upregulates OPA1 expression in resistant cells, promoting mitochondrial fusion and thereby contributing to cisplatin resistance [117]. Mitochondrial fusion has also been linked to therapy-

 doi:10.20944/preprints202605.0521.v1



induced cellular senescence. Senescence-associated secretory phenotype (SASP) can alter the tumor microenvironment and influence drug responses. Senescent cells were shown to exhibit elevated expressions of MFN1 and MFN2, indicating enhanced mitochondrial fusion. Mechanistically, these proteins promote the secretion of immunomodulatory factors such as galectin-9 into the extracellular environment, suggesting that mitochondrial fusion may influence immune cell infiltration and contribute to therapy resistance [149].

However, reduced mitochondrial fusion could also induce therapy resistance. Recent studies have shown that RANBP2-type and C3HC4-type zinc finger-containing 1 (RBCK1), an E3 ubiquitin ligase, is upregulated in ferroptosis-resistant cells and promotes the ubiquitination and proteasomal degradation of mitofusin 2 (MFN2) in Pancreatic Ductal Adenocarcinoma (PDAC) [150]. Since ferroptosis resistance represents a major obstacle in cancer therapy, loss of MFN2 reduces mitochondrial reactive oxygen species (ROS) production and lipid peroxidation, thereby inhibiting ferroptosis [150], suggesting that reduced mitochondrial fusion confers ferroptosis resistance. In another study, Actin gamma 1 (ACTG1) encodes gamma-actin, is overexpressed in various cancers, suppresses fusion by binding to MFN1, and induces cisplatin resistance [151]. Another E3 ligase, MARCH5, downregulates MFN1 via a ubiquitination-mediated mechanism, leading to mitochondrial dynamics imbalance and venetoclax resistance in multiple myeloma (MM) cells [152]. Superoxide dismutase 2 (SOD2), a mitochondrial antioxidant enzyme that scavenges ROS, has been shown to confer resistance to anlotinib in OSCC. Mechanistically, elevated SOD2 reduces ROS levels and suppresses MFN2 expression, thereby protecting mitochondria from anlotinib-induced damage and promoting anlotinib resistance [153]. Enhanced fusion serves as a convergent resistance node across apoptosis, ferroptosis, senescence, and ROS pathways. However, reduced mitochondrial fusion could also confer therapy resistance by targeting the degradation or suppression of fusion proteins (MFN1/MFN2), leading to reduced ROS and lipid peroxidation. Therefore, mitochondrial fusion thus represents a bidirectional resistance hub in cancer therapy.

### *5.2. Fission-Mediated Therapy Resistance*

In contrast to fusion, excessive mitochondrial fission is frequently associated with aggressive tumor behavior, metabolic plasticity, and resistance to anti-cancer therapies. Mitochondrial fission is largely mediated by DRP1, which is recruited to mitochondria through adaptor proteins such as FIS1 and MFF. Oncogenic mutations can influence mitochondrial fission and contribute to therapy resistance. Mutations such as NRAS $^{Q61R}$ and BRAF $^{V600E}$, which are common in melanoma and other cancers, have been associated with altered mitochondrial dynamics. Treatment with the B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) inhibitor vemurafenib has been reported to increase the expression of the fission protein DRP1 while suppressing the fusion proteins MFN1 and MFN2, indicating that mitochondrial fission may be enhanced in vemurafenib-resistant tumor cells [154]. Transcriptional regulators have also been implicated in modulating mitochondrial fission during therapy resistance. In HCC, increased Zinc Finger E-Box Binding Homeobox 1 (ZEB1) expression promotes sorafenib resistance by upregulating DRP1 [155]. Similarly, in cholangiocarcinoma (CCA), resistance to the fibroblast growth factor receptor (FGFR) inhibitor pemigatinib has been linked to increased DRP1 expression. Mechanistically, the kinase Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2) inhibits Ubiquitin-52 Amino Acid Fusion Protein (UBA52) mediated ubiquitin-mediated degradation of DRP1, leading to DRP1 stabilization and enhanced mitochondrial fission in pemigatinib-resistant cells [156]. Altered mitochondrial fission is also observed in castration-resistant prostate cancer (CRPC), an aggressive stage of prostate cancer characterized by therapeutic failure. Darolutamide-resistant cells exhibit increased DRP1 expression and reduced MFN1 levels, suggesting a shift toward enhanced mitochondrial fission [157]. In addition, androgen receptor (AR) inhibitors have been shown to suppress DRP1 phosphorylation and glycolysis; however, resistant cells restore MYC-mediated glycolytic activity along with DRP1 phosphorylation, suggesting that mitochondrial fission contributes to metabolic adaptation during resistance [158]. Mitochondrial fission also plays an important role in cancer stem cells, which are known to exhibit

 doi:10.20944/preprints202605.0521.v1



strong resistance to conventional therapies. Studies in osteosarcoma stem cells demonstrated increased DRP1 expression, indicating that enhanced mitochondrial fission may support stem-like properties and drug resistance [159]. The transcription factor Yin Yang 2 (YY2) has been reported to act as a negative regulator of mitochondrial fission by suppressing DRP1 expression, further highlighting the importance of DRP1-dependent pathways in cancer progression and resistance [160]. In addition to regulating metabolism and survival, mitochondrial fission can influence programmed cell death pathways. For example, the E3 ubiquitin ligase PJA1 promotes the degradation of PGAM5, a regulator of DRP1, thereby increasing DRP1 phosphorylation. This process suppresses ROS-mediated pyroptosis and contributes to resistance to docetaxel treatment [143].

Therefore, excessive mitochondrial fission, driven by DRP1 and its regulators (FIS1, MFF, ROCK2, PJA1), is closely linked to therapy resistance across multiple cancers. Oncogenic signals ($NRAS^{Q61R}$, $BRAF^{V600E}$, ZEB1, MYC) and kinase pathways (ROCK2) enhance DRP1 stability or expression, shifting the balance toward fission and away from fusion, thereby supporting metabolic plasticity, cancer stemness, and evasion of ROS-dependent death, such as pyroptosis. In melanoma, HCC, CCA, CRPC, and osteosarcoma, increased DRP1 and reduced MFN1/MFN2 coincide with resistance to targeted agents and chemotherapy, underscoring DRP1-dependent fission as a convergent mechanism that promotes aggressive tumor behavior and treatment failure.

### *5.3. Mitophagy and Metabolic Adaptation in Therapy Resistance*

Mitophagy, the selective autophagic removal of damaged mitochondria, represents another critical component of mitochondrial quality control that can influence cancer progression and therapeutic responses. Similar to other aspects of mitochondrial dynamics, mitophagy can function as a double-edged sword in cancer. Under metabolic stress conditions, mitophagy can promote tumor survival by maintaining mitochondrial quality and ensuring the availability of metabolic substrates required for cellular adaptation. Conversely, during early stages of tumor development, mitophagy may suppress tumorigenesis by removing dysfunctional mitochondria and limiting excessive ROS production [161]. Several studies have demonstrated that dysregulation of mitophagy contributes to therapy resistance. Therapy-induced cellular senescence has also been linked to alterations in mitochondrial dynamics and mitophagy. Treatment with 5-Fluorouracil (5-FU) can induce senescence in tumor cells, which contributes to long-term survival and relapse. Senescent cells exhibit increased expression of mitochondrial dynamics proteins, including MFN1, MFN2, FIS1, and DRP1-associated adaptor proteins, suggesting that mitochondrial remodeling may contribute to senescence-associated drug resistance [162]. Metabolic stress conditions can further influence mitochondrial dynamics and mitophagy. For example, glutamine deprivation has been shown to promote glycolytic metabolism and mitochondrial fission by phosphorylating DRP1, highlighting a link between metabolic reprogramming and mitochondrial remodeling in therapy resistance [68]. Loss of tumor suppressor proteins can also enhance mitophagy-mediated therapy resistance. Glutathione S-transferase kappa 1 (GSTK1), a mitochondrial and peroxisomal enzyme, is significantly downregulated in HCC. Loss of GSTK1 promotes mitochondrial fission and mitophagy by facilitating the interaction between PGAM5 and DRP1, thereby enhancing DRP1-mediated mitochondrial fission. Conversely, GSTK1 acts as a tumor suppressor by inhibiting mitochondrial fission by competing with DRP1 for binding to PGAM5, thereby maintaining mitochondrial quality control and inhibiting aberrant mitophagy. Dysregulation of this pathway may contribute to enhanced tumor progression and potential chemotherapy resistance in HCC [163]. Similarly, the tumor suppressor PRKAB2 is markedly reduced in renal cell carcinoma (RCC). Loss of 5′-AMP-Activated Protein Kinase, Beta-2 Subunit (PRKAB2) promotes mitophagy and contributes to resistance to tyrosine kinase inhibitors such as sunitinib. Mechanistically, PRKAB2 forms a complex with Leucine Rich Pentatricopeptide Repeat Containing (LRPPRC) and PRKN to suppress mitophagy and activate AMPK, which in turn inhibits cardiolipin biosynthesis, a lipid required for mitophagy initiation [164]. Emerging evidence further suggests that mitochondrial dynamics and mitophagy influence immune cell function within the tumor microenvironment. Excessive mitochondrial fission driven by the PGAM5–DRP1 signaling

 doi:10.20944/preprints202605.0521.v1



axis can induce mitochondrial dysfunction and promote T-cell exhaustion, thereby limiting the efficacy of cancer immunotherapy. Conversely, the E3 ubiquitin ligase Kelch Like Family Member 6 (KLHL6) helps maintain mitochondrial quality control by restraining DRP1-mediated fission and preventing terminal T-cell exhaustion, ultimately enhancing anti-tumor immune responses [165].

Mitophagy drives therapy resistance by reshaping mitochondrial quality control, dynamics, and immune crosstalk. In multiple cancers, dysregulated mitophagy often promotes mitochondrial fragmentation by disrupting tumor suppressors, such as GSTK1 or PRKAB2, thereby enhancing clearance of damaged organelles and supporting metabolic adaptation. Additionally, senescence and stress-induced shifts toward fission and mitophagy reinforce drug-resistant states. In the tumor microenvironment, excessive PGAM5-DRP1-driven fission impairs T cell function. Therefore, mitophagy modulates therapy resistance not only in cancer cells but also in the tumor microenvironment.

## 6. Therapeutic Targeting of Mitochondrial Dynamics

Targeting mitochondrial dynamics has emerged as a promising therapeutic strategy in cancer, as mitochondrial fission, fusion, and mitophagy are critical determinants of tumor cell survival, metabolism, and treatment response. Ceritinib, a tyrosine kinase inhibitor, has been reported to promote mitochondrial fission and ROS production by activating DRP1 and cleaving OPA1, without affecting MFN1 and MFN2 expression levels. Mechanistically, Ceritinib activates the mitochondrial calcium uniporter (MCU)/calpain signaling pathway, leading to OPA1 cleavage and DRP1 activation. This process ultimately suppresses thyroid cancer cell growth [166]. Piceatannol (PCT), a hydroxystilbene compound with anti-colitic properties, has also been shown to modulate mitochondrial dynamics. In chemotherapy-induced senescent CRC cells, PCT promotes mitochondrial fission by upregulating the MFF, thereby enhancing cell death [162].

OPA1 is frequently overexpressed in several cancers, including breast cancer (Figure 3), where it contributes to tumor progression and therapeutic resistance. Inhibition of OPA1 has therefore emerged as a potential anti-cancer strategy. Small-molecule inhibitors such as MYLS22 and Opitor-0 have demonstrated promising effects in breast cancer by suppressing cancer cell proliferation and migration [105]. Olaparib, an oral inhibitor of poly(ADP-ribose) polymerase (PARP) widely used in ovarian, breast, prostate, and pancreatic cancers, has also been linked to mitochondrial dynamics. Studies have shown that olaparib promotes CDK5-mediated phosphorylation of DRP1 at Serine 616, resulting in enhanced mitochondrial fission and apoptosis via caspase activation. These findings suggest that promoting mitochondrial fission may contribute to its therapeutic efficacy [167].

Mitophagy also plays a significant role in cancer progression. PINK1-mediated mitophagy is essential for the removal of damaged mitochondria and the regulation of ROS levels, thereby influencing both cell survival and death pathways. In many tumors, elevated or dysregulated mitophagy serves an oncogenic function by promoting cancer cell fitness under stress conditions. By selectively eliminating dysfunctional mitochondria, mitophagy reduces excessive ROS and prevents activation of mitochondrial-dependent cell death, allowing cancer cells to survive metabolic stress, hypoxia, and genotoxic insults such as chemotherapy or radiation [168]. Inhibition of PINK signaling has been explored as a therapeutic strategy. For example, the PINK inhibitor Quizartinib (AC220) induces ROS production, promotes TOMM20 oligomerization, and triggers BAX activation. These events lead to cytochrome c release and caspase-3 activation, followed by caspase-3–mediated cleavage of Gasodermin, ultimately inducing pyroptotic cell death [169]. Donafenib, a multikinase inhibitor approved for HCC, has also been shown to influence mitochondrial dynamics. Mechanistically, Donafenib suppresses glutathione peroxidase 4 (GPx4) expression and increases ROS production in HCC cells. In addition, it induces DRP1 expression without significantly affecting MFN1 or MFN2 levels, indicating that it promotes mitochondrial fission-mediated cell death [170].

Certain therapeutic agents may exert context-dependent effects on mitochondrial dynamics. For instance, Quercetin has demonstrated anti-cancer activity in several malignancies, including HCC. In HCC cells, Quercetin treatment promotes mitochondrial fusion by upregulating MFN1 and MFN2

 doi:10.20944/preprints202605.0521.v1



while reducing DRP1 and FIS1-mediated fission. Additionally, it enhances PINK-1 and PRKN-dependent mitophagy. Hence, quercetin-induced mitochondrial fusion and PINK1/PRKN-dependent mitophagy may negatively influence its anticancer effects in HCC. These observations suggest that combining Quercetin with mitophagy inhibitors may represent a promising therapeutic approach [171]. In some contexts, mitochondrial fusion itself can help regulate ROS production and suppress excessive mitophagy, highlighting the complexity of mitochondrial dynamics in cancer [172]. Protodioscin (PD), a steroidal saponin, has also been reported to induce apoptosis in HCC models. Mechanistically, PD enhances MFN1 expression and promotes its interaction with the pro-apoptotic protein BAK at the endoplasmic reticulum (ER), facilitating calcium influx into mitochondria and triggering apoptotic signaling [173]. Post-translational regulation of mitochondrial fusion proteins is another emerging therapeutic target. MFN1 ubiquitination is promoted by RAN-binding protein 9 (RANBP9), a core component of the C-terminal to LisH (CTLH) E3 ligase complex, with the assistance of FAM111 Trypsin Like Peptidase B (FAM111B). Targeting this pathway with glypican-3 (GPC3)-targeted lipid nanoparticles for the efficient delivery of siFAM111B has shown promising effects, promoting mitochondrial fusion and inhibiting mitophagy [174].

Similarly, E3 ubiquitin ligases such as MARCH5 can downregulate MFN1 through ubiquitination-mediated degradation, thereby disrupting mitochondrial dynamics [150]. Consequently, pharmacological activation of MFN1, for example, using leflunomide, may represent a potential therapeutic strategy in certain cancers by targeting the MARCH5-MFN2 mitochondrial axis, thereby promoting mitochondrial fusion and inhibiting mitophagy [63,152]. In addition to MFN1 and DRP1, other mitochondrial dynamics regulators such as OPA1 and MFN2 also contribute to cancer progression and therapeutic resistance. TMQ0153, a tetrahydrobenzimidazole compound, has shown promising activity in AML by reducing the expression of MFN2 and OPA1, suggesting that simultaneous targeting of these fusion proteins may provide therapeutic benefit [65]. Mitochondrial Division Inhibitor-1 (Mdivi-1) is another compound widely used to modulate mitochondrial dynamics in various diseases, including cancer. In CRC models, Mdivi-1 has been shown to decrease DRP1 protein levels while increasing MFN2 expression, thereby suppressing tumor invasion and metastasis [175]. As discussed earlier, mitophagy plays a dual role in cancer, functioning as a "double-edged sword." Depending on the cellular context, mitophagy can either promote tumor cell survival or contribute to tumor suppression. Therefore, both mitophagy inducers and inhibitors may have therapeutic potential, although their application requires careful consideration of tumor type and disease stage.

For example, Tubeimoside I has been reported to induce mitophagy via the PINK1/PRKN/MFN2 signaling pathway, thereby inhibiting AML cell proliferation [176]. Another emerging therapeutic approach involves targeting protein interactions that regulate mitochondrial fusion. AOH1996, a small-molecule inhibitor of PCNA, has been shown to disrupt the interaction between PCNA and the mitochondrial fusion protein OPA1 in AML. As PCNA stabilizes OPA1, AOH1996 disrupts this interaction, allowing the E3 ubiquitin ligase MARCH5 to ubiquitinate and degrade OPA1. This leads to reduced mitochondrial fusion and OXPHOS, ultimately suppressing the growth of leukemia stem cells (LSCs) [66]. In addition to these examples, several other compounds targeting mitochondrial dynamics regulators, including MFN1, MFN2, OPA1, DRP1, and related pathways, have been identified (Figure 5). These agents are summarized in Table 1 and highlight the growing therapeutic potential of modulating mitochondrial dynamics in cancer treatment.

**Table 1.** Various drugs related to the mitochondrial dynamics in cancer.

| Drug | Effect on mitochondrial dynamics | Type of mitochondrial dynamics | Cancer Model | References |
|---|---|---|---|---|
| Ceritinib | Increased DRP1 levels, reduced OPA1 levels | Promotes fission | Thyroid Cancer | [166] |

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| | | | | |
|---|---|---|---|---|
| Piceatannol (PCT) | Increased MFF levels, downregulated MFN1/2 | Promotes fission | CRC | [162] |
| MYLS22 | Inhibits OPA1 | Suppress the fusion | Lung and Breast Cancer | [131,177] |
| MYLS22 and Opitor-0 | Inhibits OPA1 | Suppress the fusion | Breast Cancer | [105,141] |
| Olaparib | Promotes CDK5-mediated phosphorylation of DRP1 at Serine 616 | Promotes fission | Ovarian Cancer | [167] |
| Quizartinib (AC220) | Inhibits PINK-mediated mitophagy | Inhibits mitophagy | Neuroblastoma | [169] |
| Donafenib | Induces the activation of DRP1 | Promotes fission | Liver Cancer | [170] |
| Quercetin | Increases MFN1/2 and PINK1/Parkin expression; decreases DRP1 and FIS1 expression | Promotes fusion and mitophagy | HCC, CRC | [171,178] |
| Protodioscin | Mfn1–Bak–IP3R complex formation | Promotes fission | HCC | [173] |
| Glypican-3 (GPC3)-targeted lipid nanoparticles for siFAM111B delivery | Stabilizes MFN1 levels | Promotes fusion | HCC | [174] |
| Leflunomide | Activates MFN1 | Promotes fusion | Multiple Myeloma | [152] |
| TMQ0153 | Decreased OPA1 and MFN2 expression | Promotes fission | AML | [65] |
| Mdivi.1 | Decreased DRP1 and increased MFN2 | Promotes fusion | CRC | [175] |
| Mdivi.1 | Decreased DRP1 and Increased MFN2 | Promotes fusion | Glioma | [179] |
| Tubeimoside I | Decreased MFN2 levels | Promotes Fission and mitophagy | AML | [176] |
| Ellagic Acid (EA) | Decreased MFN2 and total DRP1 levels | Promotes ROS production | Ovarian Cancer | [180] |
| ADT-OH | Decreased DRP1 and Increased MFN2 | Promotes fusion | Breast Cancer | [181] |
| Paeonol (Pae) | Increased MFN2 expression | Promotes fusion | Primary Cardiomyocytes | [182] |
| SAHA | PRKN acetylation-mediated mitophagy | Promotes mitophagy | Cervical Cancer | [183] |
| Bufalin | Affects the translocation of DRP1 and MFN2 between the cytosol and mitochondria. | Promotes fusion | Glioma | [179] |

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| | | | | |
|---|---|---|---|---|
| Onconase (ONC) | Reduced PGC1α, DRP1, and FIS1 expression | Promotes fusion | Melanoma | [184] |
| Bromoxib | Cleaves the OPA1 | Promotes fission | Leukemia, Lymphoma, and Glioblastoma | [185] |
| CTU | Promotes the OMA1 mediated OPA1 cleavage | Promotes fission | Breast Cancer | [186] |
| STM2457 | Inhibits m$^6$A modification of OPA1 | Promotes fission | CRC | [187] |
| BTM-3566<br>BTM-3528 | Promotes the OMA1 mediated OPA1 cleavage | Promotes fission | B-cell Lymphoma | [188] |
| Viriditoxin (VDT) | Cleavage of OPA1 | Promotes fission | Leukemia and Lymphoma | [189] |
| Liensinine | Dephosphorylates DRP1-Ser637 | Promotes fission | Lung adenocarcinoma | [190] |
| Ruxolitinib | Decreased total DRP1 levels | Mitochondrial dysfunction | Thyroid carcinoma | [144] |
| Nujiangexanthone A | Degrades the fusion proteins MFN1 and MFN2 | Promotes mitophagy | Cervical Cancer | [191] |
| Rosmarinic acid | Activates the DRP1 | Promotes fission | Triple Negative Breast Cancer (TNBC) | [145] |
| Reniformin A | Promotes the association of DRP1 with Bax | Mitochondrial dysfunction | TNBC | [132] |

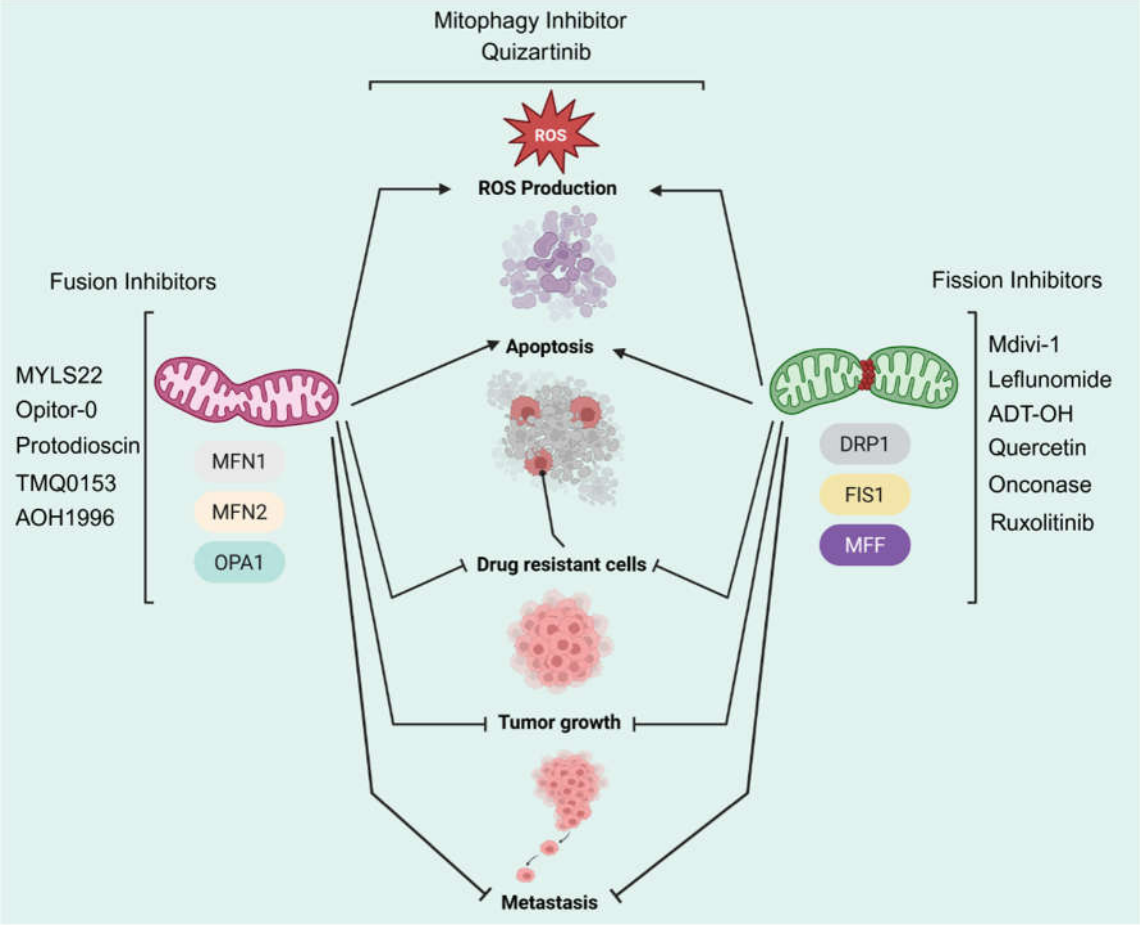

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**Figure 5.** Therapeutic targeting of mitochondrial dynamics in cancer. Recent therapeutic strategies target mitochondrial dynamics processes, including fusion, fission, and mitophagy, across various cancers. Inhibitors of mitochondrial fission, fusion, or mitophagy can increase ROS production, induce apoptosis, overcome drug resistance, suppress tumor growth and metastasis.

## 7. Conclusions and Future Directions

Despite increased understanding of mitochondrial dynamics in various cancers, many important questions remain unresolved. A deeper mechanistic understanding of how mitochondrial fission, fusion, and mitophagy coordinate with oncogenic signaling pathways will be essential for translating these findings into clinically effective therapeutic strategies. One key challenge in targeting the mitochondrial dynamics is the context-dependent role of mitochondrial dynamics machinery in cancer progression. Mitochondrial fission can promote tumor progression, metastasis, and metabolic adaptation in certain cancers, whereas in others it can trigger mitochondrial dysfunction, oxidative stress, and apoptosis. Similarly, mitochondrial fusion may support metabolic plasticity and tumor survival, and help prevent excessive mitochondrial damage by mitigating ROS accumulation. Therefore, future studies should aim to define cancer type or context-dependent mitochondrial dynamics signatures that determine whether targeting fission or fusion will provide therapeutic benefit.

Another important direction involves deciphering the interplay between mitochondrial dynamics and cancer metabolism. Mitochondrial morphology is closely linked to metabolic rewiring, including OXPHOS, glycolysis, FAO, glutaminolysis, and nucleic acid synthesis. Drug-resistant cancer cells often exhibit profound metabolic plasticity, and mitochondrial dynamics may support this plasticity. Integrative approaches combining targeted and untargeted metabolomics, such as isotope labeling experiments, mitochondrial bioenergetic profiling (OCR and EACR), and live-cell imaging using the mitochondrial tracker dyes, could provide valuable insight into how mitochondrial dynamics contribute to metabolic adaptation and therapy resistance.

Recent evidence also highlights the critical role of mitophagy in sustaining mitochondrial quality control during cancer progression and therapeutic stress. However, mitophagy emerges as a double-edged sword. While it can protect tumor cells by scavenging ROS, mitophagy is under control; excessive mitophagy may lead to bioenergetic collapse and cell death. Future research should therefore focus on identifying molecular signaling pathways that define the threshold between favorable and unfavorable mitophagy, thereby guiding the development of therapeutic strategies that selectively employ mitophagy in cancer cells.

Another encouraging area involves targeting mitochondrial dynamics to overcome therapy resistance. Many chemotherapeutic mediators and targeted therapies induce mitochondrial ROS and mitochondrial fission in cancer cells [65,130,169]. Cancer cells frequently adapt to these stresses through mitophagy to scavenge ROS, promote the expression of certain oncogenes for survival, and activate mitochondrial quality-control pathways [192]. Combining conventional anti-cancer therapies with small-molecule modulators of mitochondrial fission, fusion, or mitophagy may therefore represent a powerful strategy to re-sensitize resistant tumors. Rationally designed combination therapies that exploit mitochondrial vulnerabilities may significantly improve treatment outcomes.

Recent advances in structural biology and drug discovery technologies also open new opportunities for targeting mitochondrial dynamics proteins. High-resolution structural studies of proteins such as DRP1, OPA1, MFN1, and MFN2 are beginning to reveal potential druggable interfaces [193–196]. Structure-guided drug design, together with high-throughput chemical screening, may enable the development of highly selective inhibitors or activators with improved specificity and reduced off-target toxicity. Several drugs regulate mitochondrial dynamics through fusion, fission, or mitophagy (Table 1), and the use of these techniques will lead to the identification of lead compounds for each cancer type; further research is warranted at this stage.

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It is worth noting that mitochondrial dynamics should also be investigated within the broader context of the tumor microenvironment and cancer stem cell biology. Increasing evidence suggests that mitochondrial dynamics in immune cells, stromal cells, and CSCs may influence immune evasion, metastasis, and therapeutic response. Understanding these interactions may reveal new opportunities to integrate mitochondrial dynamics-targeted immunotherapy with microenvironment-directed therapies, thereby enabling strategies that both inhibit cancer cell growth and enhance anti-tumor activity. Advanced techniques such as multomics, single-cell sequencing, and metabolomics should be employed to accelerate progress in this field. These approaches will allow researchers to examine mitochondrial dynamics with unprecedented resolution and may uncover previously unrecognized heterogeneity in mitochondrial remodeling across tumor cell populations.

It has been observed that the mitochondrial dynamics machinery is highly overexpressed in various cancers [197] (Figure 3), and these machinery proteins can be used as biomarkers after careful investigation. More importantly, mitochondrial morphology itself may serve as a predictive biomarker of therapy resistance, helping identify tumors with distinct mitochondrial fusion, fission, or fragmentation states associated with treatment failure. In addition, biomarkers based on mitochondrial protein expression, metabolic signatures, or mitophagy activity may further improve patient stratification and help identify those most likely to benefit from therapies targeting mitochondrial dynamics.

Collectively, integrating mitochondrial biology, cancer metabolism, drug discovery, and precision oncology will be essential to translate our understanding of mitochondrial dynamics into effective cancer therapies. DRP1 inhibitors such as P110, Drpitor1, Drpitor1a, Dynasore, MIDI, and Mdivi-1 effectively block DRP1 and related dynamin family proteins. These agents show therapeutic promise across diverse pathologies—including Alzheimer's disease, acute kidney injury, and diabetes [198–201], yet their anticancer potential remains largely untapped. Future research should prioritize evaluating these inhibitors' ability to induce apoptosis via mitochondrial dynamics modulation across cancer models, potentially revealing novel vulnerabilities for clinical translation. A comprehensive understanding of the molecular mechanisms governing mitochondrial dynamics in cancer may ultimately pave the way for mitochondria-targeted therapies capable of overcoming tumor progression and therapy resistance.

**Data Availability Statement:** The data used in this article were obtained from online databases, including TIMER and GEPIA. Hence, data can be retrieved using these databases by following the references mentioned in this article.

**Acknowledgments:** We apologize to many investigators whose important works were not cited in this review due to space limitations. Duke Cancer Institute and Grant IRG-23-1077679-01-IRG from the American Cancer Society partly support this work for C.-C.H.

**Declaration of Competing Interest:** All other authors have declared that no competing interests exist.

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