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REVIEW ARTICLE

Convergence of epithelial-mesenchymal transition and mitochondrial dynamics: Mechanisms and therapeutic opportunities in cancer metastasis

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Abstract

Epithelial-mesenchymal transition (EMT) is a biological process in which epithelial cells acquire mesenchymal characteristics, including enhanced motility. While EMT plays essential roles in embryonic development and tissue repair, its dysregulation is closely associated with cancer metastasis and fibrotic diseases. The active and context-dependent energy demands of EMT highlight the importance of mitochondrial function and dynamics, particularly mitochondrial fusion and fission, in facilitating EMT. Recent findings reveal a critical yet underexplored role of mitochondrial dynamics, especially fusion and fission, in supporting EMT and cancer metastasis through metabolic reprogramming and redox signaling. Dysregulation of mitochondrial dynamics has been implicated in EMT-related diseases, especially cancer and fibrosis, both of which share common pathological features such as chronic inflammation, extracellular matrix remodeling, and sustained EMT activation. Despite growing interest, the intersection of mitochondrial dynamics, stress responses, and EMT remains insufficiently studied, particularly in the context of progressive diseases such as cancer. This review addresses this gap by exploring the interplay between mitochondrial dynamics and EMT in cancer metastasis, highlighting potential vulnerabilities and therapeutic opportunities. Understanding the convergence of EMT and mitochondrial dynamics offers a novel perspective on cancer progression and paves the way for targeted interventions. Moreover, the study of mitochondrial dynamics in fibrosis may provide insights for therapeutic strategies against cancer metastasis.

Keywords: Mitochondrial dynamics; Mitochondrial fusion; Mitochondrial fission; Epithelial-mesenchymal transition; Cancer; Fibrosis

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1. Introduction

Epithelial-mesenchymal transition (EMT) is a tightly regulated biological process in which epithelial cells lose their polarity and cell-cell adhesion characteristics, adopting a mesenchymal phenotype that is more motile and invasive.[1] EMT was first documented by Elizabeth Hay in 1995 during her research on chick primitive streak formation.[2] Since then, it has been recognized as a fundamental process involved in embryonic

development, wound healing, fibrosis, and tumor progression.[3-5] EMT is categorized into three different types depending on its physiological and pathological contexts. Type 1 EMT occurs during embryogenesis and is required for mesoderm and endoderm layer formation, leading to organogenesis and tissue differentiation.[5-7] Transcription factors such as SNAIL, SLUG, and TWIST regulate the process by controlling cell polarity and adhesion dynamics.[8] Signaling pathways including transforming growth factor (TGF)-β, Wnt, and Notch play crucial roles in initiating and maintaining EMT during development.[9,10] Type 2 EMT is associated with tissue repair and fibrosis, where epithelial cells undergo transdifferentiation into myofibroblasts in response to injury and chronic inflammation. Although this process supports wound healing, its dysregulation leads to fibrotic diseases such as pulmonary, renal, optic, and hepatic fibrosis.[5,11,12] Type 3 EMT plays a role in cancer development and metastasis, allowing tumor cells to acquire invasive and stem cell-like characteristics.[13,14] EMT-promoting transcription factors such as SNAIL, TWIST, and ZEB are often overexpressed in many cancers, promoting tumor spread and drug resistance.[8,15]

Understanding EMT and its regulation by tumor microenvironmental factors, such as hypoxia, immune evasion, and stromal interactions, is essential for developing targeted anti-metastatic therapies.[16-18] An important but frequently overlooked feature of EMT is its context-dependent energy requirement, which is regulated through mitochondrial function and dynamics.[19,20] EMT induces metabolic reprogramming and shifts between glycolysis and oxidative phosphorylation (OXPHOS), enabling cells to meet the energy demands necessary for migration, invasion, and survival. Reactive oxygen species (ROS) play a key role in EMT signaling pathways.[21,22] While glycolysis provides a temporary energy supply during cellular transitions, OXPHOS ensures sustained adenosine triphosphate (ATP) production, and mitochondrial biogenesis adapts to expanding metabolic needs.[23-25] Mitochondrial ROS function as signaling molecules for EMT by activating key transcription factors and stabilizing hypoxia-inducible factor-1α (HIF-1α), subsequently leading to glycolytic metabolism.[26-28]

Mitochondria, with their characteristic double-membrane structure, are essential for cellular energy homeostasis, metabolism, health, and apoptosis.[29-34] These maternally inherited, versatile cytoplasmic organelles represent an evolutionary adaptation to mitigate the higher mutational load associated with paternal gametes.[35,36] This uniparental mode of inheritance is essential for maintaining genetic stability across generations, minimizing mutational burden, and enhancing the overall population fitness and viability.[37] In addition to ATP generation, mitochondria regulate redox balance, metabolic waste disposal, immunity, and cell fate determination.[29,38-40] Their dynamic nature, governed by the processes of fusion and fission, is essential for maintaining mitochondrial integrity and function.[41]

Mitochondrial fusion permits the exchange of mitochondrial contents, preventing damage and maintaining functional capability.[42] Fission, on the other hand, promotes the segregation and removal of damaged mitochondria through mitophagy, thereby maintaining cellular homeostasis.[43] Fusion and fission are tightly regulated during EMT to accommodate the altered bioenergetic and metabolic demands of transitioning cells.[44] The relationship between mitochondrial dynamics and EMT is depicted in Figure 1.

The dysregulation of mitochondrial dynamics has a profound impact on EMT-related pathologies.[45] Among EMT-related disorders, cancer and fibrosis are two significant pathological processes that account for a significant portion of global morbidity and mortality.[46-48] In cancer, mitochondrial dynamics influence metastatic potential, with increased mitochondrial fission promoting invasion and drug resistance.[49,50] In fibrotic disorders, mitochondrial dysfunction is responsible for the sustained activation of myofibroblasts and the excessive extracellular matrix secretion, leading to progressive tissue fibrosis.[51,52]

There is growing research interest in understanding the relationship between mitochondrial dynamics and disease progression. While recent studies have explored mitochondrial quality control in relation to EMT, these findings remain fragmented and lack a unified analysis within specific disease contexts.[53,54] Although several reviews have addressed mitochondrial dynamics in cancer or fibrosis separately, most focus on fusion-fission mechanisms and their roles across diseases or emphasize specific cancer types, without offering broader, integrative insights and often lacking incorporation of recent data.[49,50,55-67] To the best of our knowledge, no comprehensive review to date has examined both mitochondrial dynamics and EMT together, despite cancer and fibrosis sharing common molecular mechanisms such as chronic inflammation, extracellular matrix remodeling, and sustained EMT – processes intimately regulated by mitochondria.[68,69]

This review aims to address this gap by exploring how mitochondrial dynamics intersect with EMT in both cancer and fibrosis to drive disease severity, progression, and therapy resistance. Cancer and fibrosis are inextricably linked, as fibrotic environments can promote tumor initiation and progression, while cancerous tissues often exhibit fibrotic remodeling that supports malignancy.

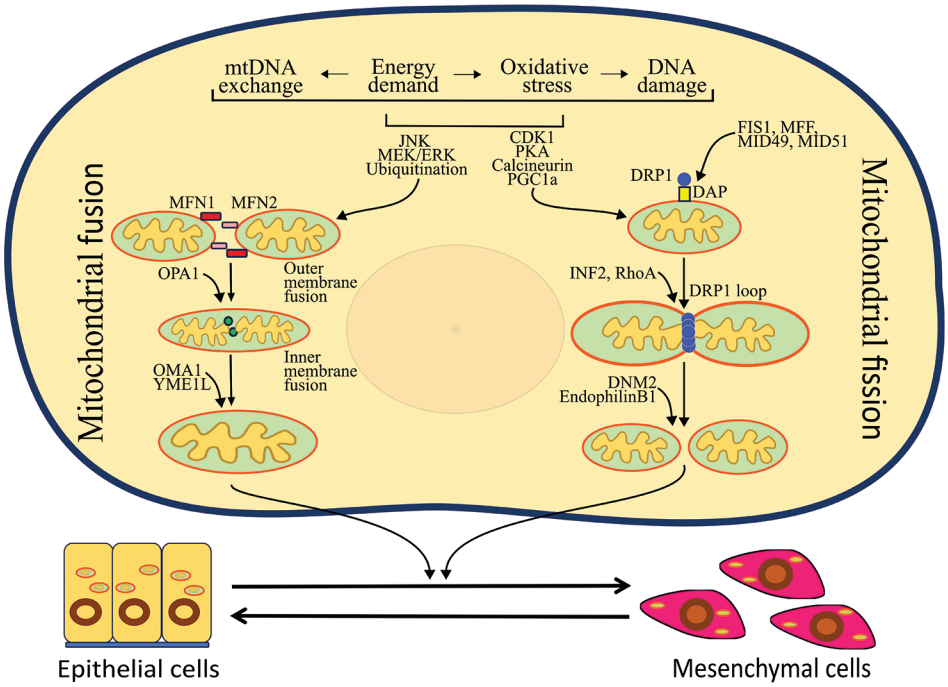

Figure 1. Association of mitochondrial dynamics with epithelial-mesenchymal transition. Mitochondrial fusion is mediated by mitofusin1 (MFN1) and mitofusin2 (MFN2) for the outer membrane, and optic atrophy 1 (OPA1) for inner membrane. Upstream regulators such as JNK, MEK/ERK signaling, along with post-translational modifications through ubiquitination, contribute to MFN degradation and deactivation. Conversely, mitochondrial fission involves dynamin-related protein 1 (DRP1) and its adaptor proteins (DAP), including FIS1, mitochondrial fission factor (MFF), and mitochondrial dynamics proteins 49 and 51 (MID49 and MID51). Additional fission modulators, such as INF2, RhoA, endophilin B1, and dynamin (DNM) 2, facilitate mitochondrial constriction and division. Image created by authors using Inkscape drawing software.
Abbreviations: CDK1: Cyclin-dependent kinase 1; ERK: Extracellular signal-regulated kinase; INF2: Inverted formin 2; JNK: c-Jun N-terminal kinase; MEK: Mitogen-activated protein kinase kinase; mtDNA: Mitochondrial DNA; OMA1: OMA1 zinc metallopeptidase; PGC-1a: Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PKA: Protein kinase A; RhoA: Ras homolog family member A; YME1L: YME1-like 1 ATPase.

For example, intratumoral fibrosis promotes renal cancer aggressiveness through extracellular matrix remodeling and pro-tumorigenic signaling,[70] and idiopathic pulmonary fibrosis (IPF) is associated with increased incidence of lung cancer, with overlapping fibrogenic and oncogenic pathways that complicate clinical management.[71] Similarly, chronic liver fibrosis contributes to hepatocellular carcinoma (HCC) through sustained inflammation and cellular transformation.[72] By investigating these conditions together, we can identify shared mitochondrial vulnerabilities that may serve as effective therapeutic targets, potentially advancing the development of interventions beneficial to both cancer and fibrotic diseases. The increasing recognition of mitochondria as therapeutic targets highlights the utility of such multidisciplinary approaches, particularly in diseases involving repeted EMT activity.

2. Mitochondrial fission

Mitochondrial fission is a highly regulated and complex process that divides a single mitochondrion into two daughter mitochondria.[62] This dynamic event is not merely a structural transformation – it is an intrinsic cellular process critical for various physiological functions, such as cell division (to ensure the transmission of mitochondria to daughter cells),[73,74] mitochondrial quality control via mitophagy,[75] adaptation to energy demands,[20,61] and apoptosis.[76] Dysregulation of mitochondrial fission has been associated with various pathological conditions, including cancer, fibrosis, neurodegenerative diseases, and cardiovascular diseases.[61,77-80]

2.1. Molecular machinery of mitochondrial fission

The primary inducer of mitochondrial fission is dynamin-related protein 1 (DRP1), a cytosolic GTPase belonging to the dynamin superfamily.[81,82] The process begins with the recruitment of DRP1 from the cytoplasm to the outer mitochondrial membrane (OMM), a step essential for mitochondrial division.[43] This recruitment is mediated by several DRP1 adaptor proteins, including fission protein 1 (FIS1), mitochondrial fission factor (MFF), and mitochondrial dynamics proteins 49 and 51.[82-84] These

proteins regulate DRP1 recruitment, oligomerization, and GTPase activity, forming the functional fission apparatus.[59]

Once recruited, DRP1 oligomerizes into loop-like structures at predefined mitochondrial fission sites.[85,86] Following oligomerization, DRP1 undergoes GTP hydrolysis, inducing conformational changes that progressively constrict the mitochondrial membrane.[87,88] This constriction is further supported by actin filaments, which facilitate DRP1 recruitment and membrane remodeling. Actin polymerization at fission sites is regulated by proteins such as inverted formin 2 and Ras homolog (Rho) GTPases, including Rho family member A (RhoA), which enhance DRP1 activity.[62,89-91] In addition, the endoplasmic reticulum forms contact sites with mitochondria, marking future fission locations and aiding in membrane constriction.[92]

While DRP1 plays a key role in mitochondrial constriction, complete membrane scission often requires additional factors. Dynamin 2 and endophilin B1 facilitate the final separation of both outer and inner mitochondrial membranes (IMM), ensuring successful mitochondrial division.[81,93] Following fission, the newly divided mitochondria undergo structural and functional remodeling to redistribute mitochondrial DNA (mtDNA), proteins, and lipids, thereby maintaining cellular energy homeostasis.[19,84]

2.2. Regulation of mitochondrial fission

The GTPase DRP1 serves as a central effector of mitochondrial fission, and its activity is finely modulated through a variety of post-translational modifications (PTMs) that allow the cell to rapidly respond to physiological and pathological cues. Phosphorylation is one of the most prominent regulatory mechanisms. For example, cyclin-dependent kinase (CDK)1/cyclin B1 phosphorylates DRP1 at serine 616 during mitosis, recruiting it to the OMM and facilitating mitochondrial division necessary for equal organelle inheritance during cell division.[94,95] In neurons, CDK5-mediated phosphorylation plays a dual role – it contributes to neuronal apoptosis under stress conditions,[96] yet also appears to inhibit premature fission during neuronal maturation,[97] suggesting context-specific modulation. PKA-dependent phosphorylation at serine 637 leads to DRP1 inactivation, mitochondrial elongation, and cytoprotective effects through reduced apoptosis, an effect reversible by calcineurin-mediated dephosphorylation.[98,99] Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) 2 has been shown to phosphorylate DRP1 at serine 616 in cancer cells, promoting mitochondrial fragmentation and driving proliferation and tumorigenesis.[100] Similarly, stress-activated kinases such as rho-associated, coiled-coil-containing protein kinase 1, and glycogen synthase kinase-3 beta phosphorylate DRP1 under hyperglycemic and Alzheimer's disease conditions, respectively, exacerbating mitochondrial fragmentation, ROS production, and cell death.[101,102]

Beyond phosphorylation, DRP1 is regulated by ubiquitination, primarily through the mitochondrial E3 ligases (mitochondrial ubiquitin ligase membrane-associated RING-CH [MARCH[5] and Parkin), which mediate either its stabilization at the OMM or degradation through the proteasome. MARCH5, in particular, modulates mitochondrial morphology by regulating the balance between DRP1 and mitofusins (MFNs),[103,104] while Parkin targets DRP1 for ubiquitination during mitochondrial quality control responses, including mitophagy.[105] Furthermore, SUMOylation of DRP1 by small ubiquitin-like modifier (SUMO) 1 enhances its retention on mitochondria and promotes fission, particularly during apoptosis.[106] This modification is reversed by sentrin/SUMO-specific proteases (SENPs), notably SENP3 and SENP5, which regulate the balance between SUMOylated and deSUMOylated DRP1 during mitochondrial stress and ischemic injury.[107,108] Notably, Bcl-2-associated X protein/BAK-dependent signals have been implicated in increasing DRP1 SUMOylation during apoptotic progression.[109] Collectively, these layers of regulation highlight DRP1 as a versatile node in cellular signaling networks that couple mitochondrial dynamics to proliferation, differentiation, stress adaptation, and cell death.

While this dynamic remodeling is essential for mitochondrial inheritance and adaptation to cellular needs, dysregulation of this balance, particularly increased mitochondrial fission, is increasingly recognized for its role in cancer. Aberrant DRP1 activation and the resulting excessive mitochondrial fragmentation have been implicated in promoting cancer cell proliferation, metastasis, and chemoresistance.[110,111] Therefore, understanding the precise regulation of mitochondrial fission is crucial for elucidating its contribution to cancer development and identifying potential therapeutic targets.

2.3. Mitochondrial fission and cancer

In cancer, enhanced mitochondrial fission is usually present and contributes to the Warburg effect (increased glycolysis),[112,113] apoptosis evasion,[114] and enhanced metastatic potential.[110] Within the complex field of cancer biology, mitochondrial fission plays a multifaceted and often pro-tumorigenic role.[110] Cancer cells exploit dysregulated fission to enhance survival, growth, and metastatic capacity. One of the primary ways mitochondrial fission

promotes that cancer development is through metabolic reprogramming, that is, the enhancement of glycolysis, known as the Warburg effect.[21,115,116] This metabolic shift, whereby cancer cells rely on glycolysis to generate energy even under normoxic conditions, provides a rapid source of ATP and metabolic intermediates essential for accelerated cellular proliferation and tumor growth.[117-119] Increased mitochondrial fission may also help maintain hypoxic conditions in the tumor microenvironment and vice versa.[120] Hypoxia, in turn, can promote angiogenesis, further supporting tumor growth and survival.[121-123] Furthermore, abnormal mitochondrial fission enables cancer cells to evade apoptosis,[124] a capability that is especially significant in aggressive and metastatic cancers. By enhancing cellular motility and migration, mitochondrial fission contributes to cancer invasiveness. Due to its crucial role in cancer development, mitochondrial fission has been identified as a potential target for therapeutic intervention. Consequently, considerable research efforts are focused on synthesizing and evaluating DRP1 inhibitors, which serve as key regulators of mitochondrial fission, often in combination with other components of the fission machinery. These therapeutic strategies aim to interfere with malignancy-associated metabolic processes, restore normal mitochondrial dynamics and function, and ultimately promote cancer cell apoptosis, thereby enhancing treatment outcomes.

2.3.1. Mitochondrial fission in HCC

Mitochondrial fission, primarily regulated by DRP1, plays a critical role in the progression of HCC by promotingtumor growth, metabolic reprogramming, and immune evasion. Overexpression of DRP1 in HCC tissues correlates with mitochondrial fragmentation, increased tumors aggressiveness, and poor prognosis.[125]

DRP1-induced mitochondrial fission elevates ROS production, which activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and inhibits tumor suppressor p53, thereby promoting HCC cell survival and proliferation.[126,127] Downregulation of general control of amino acid synthesis 5-like 1, a mitochondrial protein, in metastatic HCC tissues has been shown to increase ROS production through fatty acid oxidation (FAO), further activating ERK and DRP1 pathways and promoting EMT.[128] Palmitate and carnitine-induced FAO stimulates mitochondrial fission and EMT-related gene expression, promoting HCC cell migration.[128]

The long non-coding RNA (lncRNA) LL22NC03-N14H11.1, overexpressed in HCC, enhances cell proliferation, migration, and invasion by stimulating mitochondrial fission through the MAPK/ERK1/2 pathway. This effect is DRP1-dependent, highlighting its involvement in HCC metastasis.[128] As shown in Figure 2, LL22NC03-N14H11.1 activates the proto-oncogene c-Myb, which suppresses the transcription of leucine zipper-like transcription regulator 1 (LZTR1). The reduction in LZTR1 impairs the ubiquitination of H-RAS, activating the MAPK pathway and leading to *DRP1* phosphorylation at serine 616, thus enhancing mitochondrial fission.[129]

Similarly, the proviral integration site for Moloney murine leukemia virus 1 (PIM1) kinase, a serine/threonine proto-oncogene overexpressed in several cancers,[130,131] modulates mitochondrial dynamics by promoting cytoplasmic expression of RNA-binding motif protein Y-linked (RBMY). This action inhibits apoptosis and enhances mitochondrial function by elevating ATP and ROS production.[132] Increased ROS levels drive DRP1-regulated mitochondrial fission, enhancing metabolic adaptability and invasiveness of HCC cells. RBMY also upregulates EMT markers such as SNAIL1 and ZEB1, further advancing metastasis. Importantly, the inhibition of either PIM1 or DRP1 substantially reduces RBMY expression, mitochondrial fission, EMT, and metastatic activity.[132] The relationship between mitochondrial fission and HCC is illustrated in Figure 2. Given the central role of mitochondrial fission in HCC, pharmacological inhibition of DRP1 using agents such as mitochondrial division inhibitor (Mdivi-1) has been shown to suppress tumor growth and metastatic dissemination.[126]

2.3.2. Mitochondrial fission in ovarian cancer

Mitochondrial fission plays a significant role in ovarian cancer development and controls tumor cell proliferation, metastasis, and EMT through remodeled metabolism and mitochondrial dynamics. Salt-inducible kinase 2 (SIK2), a member of the adenosine monophosphate-activated protein kinase family,[133] has been shown to augment the Warburg effect by enhancing HIF-1α expression through the phosphoinositide 3-kinase/protein kinase B (AKT) signaling pathway, thus promoting glycolysis under aerobic conditions. As shown in Figure 3, SIK2 also supports mitochondrial fission by promoting phosphorylation of *DRP1* at serine 616, thereby suppressing OXPHOS. This dual mechanism of metabolic reprogramming and mitochondrial fragmentation contributes to tumor growth, EMT, and metastasis.[117]

Similarly, the transcription factor E26 transformation-specific sequence 1, a proto-oncogenic regulator, promotes EMT and metastasis in various cancers by modulating EMT-related transcription factors.[134] It also regulates mitochondrial fission through DRP1 activation, leading to increased mitochondrial fragmentation and a metabolic

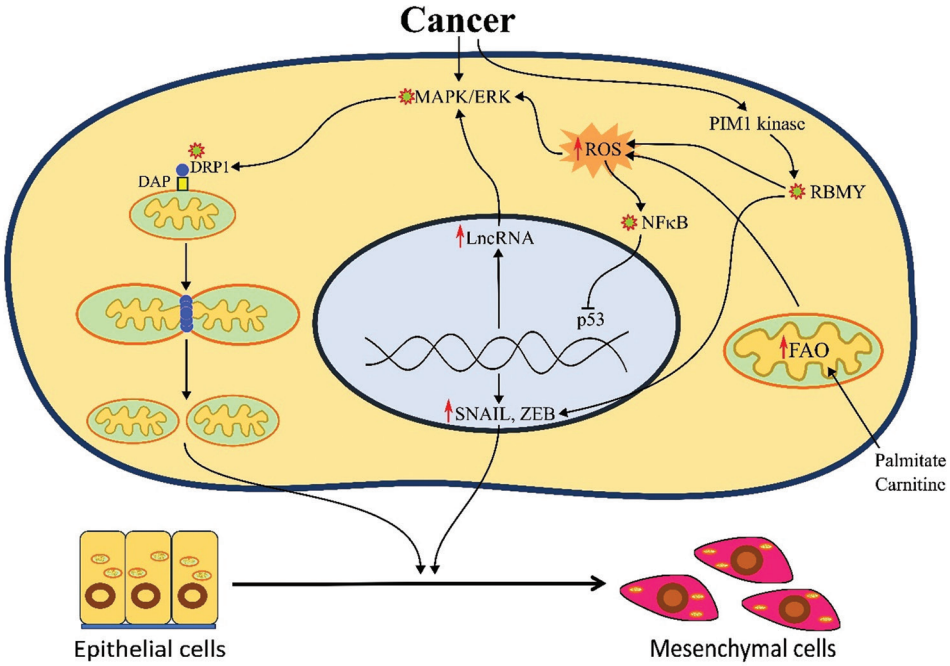

Figure 2. Mitochondrial fission in hepatocellular carcinoma (HCC) and its association with epithelial–mesenchymal transition (EMT). Proviral integration site for Moloney murine leukemia virus 1 (PIM1) kinase phosphorylates RNA-binding motif protein Y-linked (RBMY), leading to elevated reactivate oxygen species (ROS) levels. Increased fatty acid oxidation also contributes to ROS production. ROS activates the MAPK/ERK pathway, which phosphorylates and activates dynamic related protein 1 (DRP1), a central mediator of mitochondrial fission. Long non-coding RNAs (lncRNAs) further enhance MAPK/ERK signaling, reinforcing DRP1 activation. In addition, ROS activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which suppresses p53, promoting tumor survival. RBMY also upregulates transcription factors SNAIL and ZEB, thereby promoting EMT. Together, these pathways converge to increase mitochondrial fragmentation, support metabolic reprogramming, and drive tumor progression in HCC. Image created by authors using Inkscape drawing software.
Abbreviations: DAP: DRP adaptor protein; ERK: Extracellular signal-regulated kinase; MAPK: Mitogen-activated protein kinase; p53: Tumor suppressor.

transition toward glycolysis (Figure 3). This process enhances the invasiveness of ovarian cancer cells and supports EMT. Notably, DRP1 inhibition through gene silencing or pharmacological agents such as Mdivi-1 significantly reduces metastatic activity in ovarian cancer cells.[135] Sirtuin 6 (SIRT6), a nicotinamide adenine dinucleotide-dependent deacetylase with dual roles in cancers, also regulates mitochondrial fission and cellular invasiveness. It modulates glycolysis and OXPHOS, increasing invadopodia formation through actin cytoskeleton reorganization. This effect is mediated by ERK1/2-dependent phosphorylation of *DRP1* at serine 616, resulting in mitochondrial fragmentation and increased motility of cancer cells. Silencing SIRT6 with small interfering RNA significantly reduces mitochondrial fission, stress fiber formation, and cellular invasion, emphasizing its role in metastasis.[136,137] The relationship between mitochondrial fission and ovarian cancer is illustrated in Figure 3.

2.3.3. Mitochondrial fission in breast cancer

Mitochondrial fission plays a multifaceted and context-dependent role in breast cancer, influencing tumor growth, metabolic behavior, and metastatic potential. The balance between mitochondrial fusion and fission is especially important in regulating cancer cell behavior, particularly in aggressive subtypes such as triple-negative breast cancer (TNBC). In breast cancer cells, mitochondrial fission has been shown to be essential for efficient migration and invasion, highlighting the critical role of mitochondrial dynamics in supporting metastatic activity.[138] A systematic review by Xing *et al.*[139] underscored the complex interplay between fission and fusion in breast cancer. Their results showed that although mitochondrial fission is generally implicated in cancer progression, in certain TNBC subtypes, increased fission inhibits oncogenic signaling pathways and metastasis. Specifically, enforced mitochondrial fission was found to suppress AKT and ERK signaling, two pathways crucial for cancer cell survival and proliferation. As a result, both chemical and genetic induction of mitochondrial fission led to reduced migration, invasion, and metastasis.[139] In contrast, leflunomide, a mitochondrial fusion-inducing drug, reversed these effects by restoring migratory behavior, oncogenic signaling, and metastatic capacity.[140] Importantly, higher expression of genes

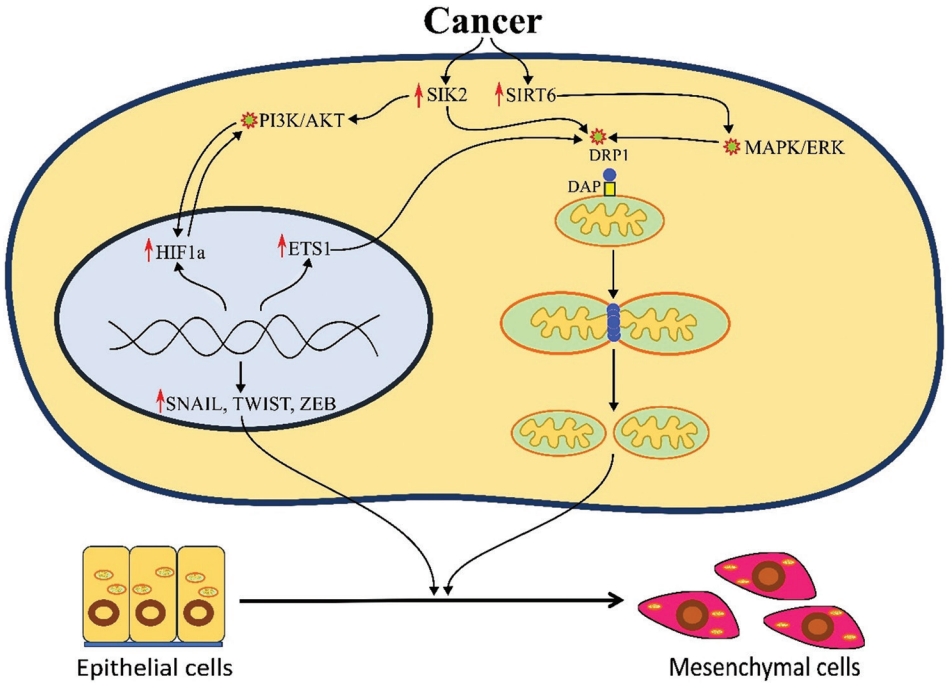

Figure 3. Mitochondrial fission in ovarian carcinoma and its association with epithelial-mesenchymal transition (EMT). Salt-inducible kinase 2 (SIK2) enhances glycolysis by upregulating hypoxia-inducible factor 1α (HIF-1α) through activation of the PI3K/AKT signaling pathway and promotes mitochondrial fission by phosphorylating dynamin-related protein 1 (DRP1) at serine 616, thereby amplifying the Warburg effect. E26 transformation-specific sequence 1 (ETS1), a proto-oncogenic transcription factor, facilitates EMT and cellular invasion by activating EMT-related genes and inducing DRP1-mediated mitochondrial fragmentation. SIRT6, often upregulated in cancer, contributes to tumor growth, EMT, and metastasis through MAPK/ERK-dependent phosphorylation of *DRP1*. Image created by authors using Inkscape drawing software.
Abbreviation: DAP: DRP adaptor protein; ERK: Extracellular signal-regulated kinase; MAPK: Mitogen-activated protein kinase; SIRT6: Sirtuin 6.

involved in mitochondrial fission has been associated with improved survival in some breast cancer patients, suggesting a possible protective effect of fission under specific conditions. Kuang *et al.*[141] further explored the broad clinical implications of disrupted mitochondrial dynamics in breast cancer, emphasizing their relevance in diagnosis, prognosis, and therapeutic strategies. Their findings confirm that alterations in mitochondrial fission and fusion significantly impact tumor aggressiveness and treatment outcomes, reinforcing the therapeutic potential of targeting mitochondrial dynamics.

2.3.4. Mitochondrial fission in oral squamous cell carcinoma (OSCC)

Mitochondrial fission is a key event in the progression and metastasis of OSCC. Figure 4 illustrates the association between mitochondrial fission and EMT in OSSC. Overexpression of interferon regulatory factor 2 binding protein 2 (IRF2BP2) induces mitochondrial fission through enhanced phosphorylation and mitochondrial localization of DRP1. This activity stimulates FAO to provide energy for cancer cells and promotes invasion, lymphatic vessel infiltration, and EMT. Silencing IRF2BP2 downregulates carnitine palmitoyl transferase 1A (CPT1A), a central enzyme in FAO, thereby suppressing these processes. Conversely, overexpression of CPT1A restores invasive and EMT activities, establishing the connection between IRF2BP2, mitochondrial fission, FAO, and metastasis.[142]

Inhibition of DRP1 results in mitochondrial elongation of, shifting the balance away from fission. Elongated mitochondria correlates with reduced cancer stemness, decreased cluster of differentiation 44 and aldehyde dehydrogenase 1 expression, and enhanced glutaminolysis. This metabolic alteration also induces ferroptosis, an iron-catalyzed, lipid-peroxidation-dependent form of programmed cell death, which is reversed on DRP1 activation. Furthermore, DRP1 inhibition suppresses OSCC cell invasion and migration, suggesting that targeting mitochondrial dynamics may be an effective anti-tumor strategy (Figure 4).[143]

Mitochondrial fission plays a biphasic role in OSCC. ROS1, a receptor tyrosine kinase typically located on the plasma membrane, translocates to the mitochondria in cancer cells, where it mediates mitochondrial fission and enhances OXPHOS and ATP levels in highly invasive

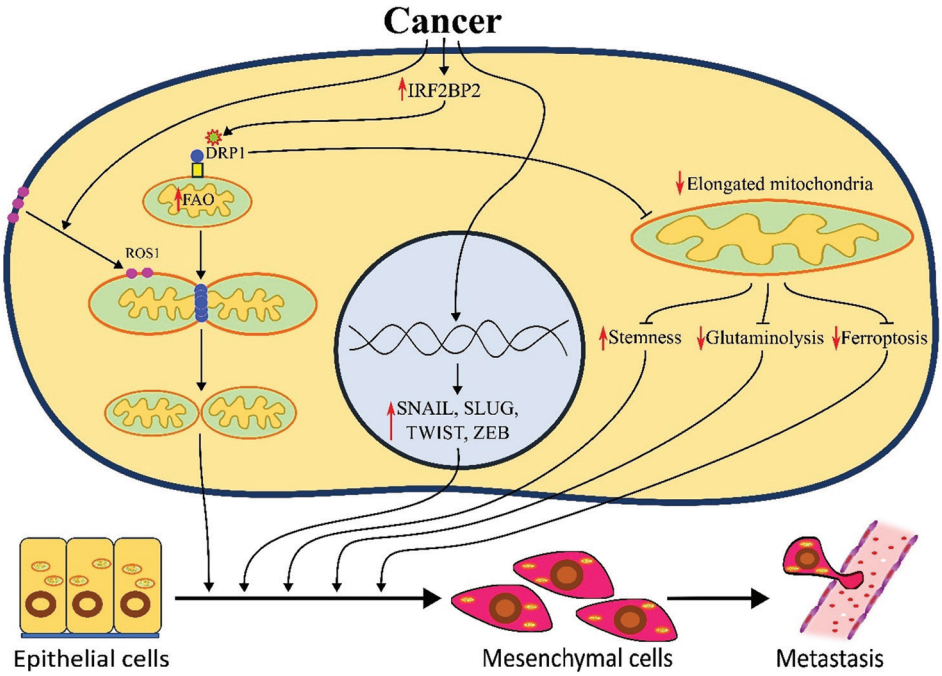

Figure 4. Association of mitochondrial fission in oral squamous cell carcinoma (OSCC) with epithelial-mesenchymal transition (EMT). Interferon regulatory factor 2 binding protein 2 (IRF2BP2), overexpressed in OSCC, promotes dynamin-related protein 1 (DRP1)-mediated fission, enhancing fatty acid oxidation and driving invasion and EMT. DRP1 activation reduces mitochondrial elongation, increases stemness markers, suppresses ferroptosis and glutaminolysis, and facilitates invasion. ROS1, a receptor tyrosine kinase, translocates to the mitochondria in aggressive OSCC cells, triggering fission and boosting oxidative phosphorylation and adenosine triphosphate production to sustain oncogenic signaling. EMT promotes the transition from an epithelial to a mesenchymal state, supportingmetastasis. Image created by the authors using Inkscape drawing software.
Abbreviation: FAO: Fatty acid oxidation.

OSCC cells (Figure 4). This metabolic reprogramming further activates oncogenic signaling pathways that sustain tumor growth.[144,145] Excessive fission drives ATP production, promoting proliferation and invasion; however, inhibition of DRP1 using Mdivi-1 induces apoptosis and improves immunotherapy efficacy by increasing major histocompatibility complex class I expression.[146] Moreover, in head and neck squamous cell carcinoma (HNSCC), hypoxia-induced ROS promote mitochondrial fission through HIF-1α-mediated upregulation of MFF, thereby enhancing cisplatin chemosensitivity.[147] Overexpression of Hippo/mammalian sterile 20-like kinase 1 further induces mitochondrial-dependent cell death through activation of the β-catenin/DRP1 pathway, highlighting the therapeutic potential of targeting mitochondrial dynamics in HNSCC.[148] In addition, lncRNAs such as microRNA processing-related lncRNA and cisplatin-sensitivity-associated lncRNA regulate mitochondrial fission, cisplatin sensitivity, and apoptosis in squamous cell carcinoma. LncRNAs are non-protein-coding RNA molecules that modulate gene expression at various levels, including transcriptional, post-transcriptional, and epigenetic regulation. By interacting with chromatin, transcription factors, or RNA-binding proteins, lncRNAs influence critical cellular processes such as the cell cycle, apoptosis, and metastasis. In cancer, dysregulated lncRNA expression is often associated with poor prognosis, resistance to chemotherapy, and metastasis, underscoring their emerging role as potential therapeutic targets.[149-152] The relationship between mitochondrial fission and OSSC is depicted in Figure 4.

2.3.5. Mitochondrial fission in other malignancies

Beyond the specific cancers previously discussed, mitochondrial fission plays diverse and context-dependent roles in various other malignancies. These roles often involve complex interactions with key cellular pathways and can have both pro- and anti-tumorigenic effects, highlighting the need for careful consideration of specific cancer types and molecular contexts when developing therapeutic strategies.

The tumor suppressor protein p53 plays a critical role in modulating mitochondrial dynamics to prevent cancer cell spread and invasion.[153] Elevated p53 levels promote mitochondrial elongation and attenuate invasive cell migration by reducing DRP1-mediated mitochondrial

fission. This regulation involves diminishing mammalian target of rapamycin complex 1 (mTORC1)-controlled mitochondrial fission process 1 protein (MTFP1) protein levels, which, in turn, attenuates DRP1-driven mitochondrial fission and invasive cell migration. The activation of the mTORC1/MTFP1/DRP1/ERK1/2 signaling axis is required for the EMT switch, matrix metalloproteinase-9 elevation, and cancer dissemination on loss of wild type p53. Thus, by maintaining a balance between fission and fusion, p53 ensures mitochondrial homeostasis, which is crucial for cellular energy production and the reduction of oxidative stress. Loss of p53 disrupts this balance, leading to increased mitochondrial fission, enhanced cell motility, and invasion, thereby promoting cancer progression.

In endometrial cancer, DRP1-driven mitochondrial fission mediates high glucose-induced mitochondrial dysfunction and EMT.[154] Exposure to a high glucose environment significantly increases DRP1 activation, leading to mitochondrial dysfunction and an imbalance in mitochondrial homeostasis. This imbalance results in altered glucose metabolism, promoting increased EMT, cell migration, and invasion. Drp1 RNA interference has been shown to inhibit cell cycle progression induced by high glucose, highlighting the critical role of DRP1 in these processes. The knockdown of *Drp1* can partially alleviate these detrimental changes, suggesting that targeting DRP1 may offer a potential therapeutic strategy for treating endometrial cancer, particularly in patients with diabetes.

In thyroid cancer, inhibiting mitochondrial fission with Mdivi-1, a DRP1 inhibitor, reduces cell proliferation and invasiveness.[155,156] Studies have shown that Mdivi-1 inhibits cell proliferation and EMT by modulating the NF-κB pathway. Mdivi-1 effectively reduces mitochondrial fission, thereby decreasing the invasiveness of thyroid cancer cells. By inhibiting DRP1-mediated fission, Mdivi-1 helps preserve mitochondrial function. In oncocytic thyroid tumors, *DRP1* overexpression promotes mitochondrial fission and enhances cancer cell migration, suggesting DRP1 as a potential therapeutic target.[157]

In stomach adenocarcinoma, the GLI family zinc finger 2 (GLI2)/cadherin 6 (CDH6) axis enhances mitochondrial fission and cancer cell invasiveness.[158] The GLI2 transcription factor upregulates CDH6, enhancing the migratory and invasive abilities of stomach adenocarcinoma cells. This axis promotes mitochondrial fission by increasing *DRP1* expression, which is associated with enhanced cancer cell motility and invasiveness.

Mitochondrial fission sits at a crossroads in cancer biology, sometimes fueling tumor growth and spread, while in other contexts, its inhibition can suppress malignancy. This duality reminds us that cancer cells, like all living systems, finely tune their organelles to meet changing demands. While DRP1 and its regulation present promising therapeutic targets, the variability across cancer types necessitates cancer-specific therapies. Mitochondrial fragmentation appears to aid cancer cells in coping with metabolic stress and hypoxia, further supporting their survival in hostile tumor microenvironments. Indiscriminate inhibition of mitochondrial fission risks disturbing physiological mitochondrial quality control in healthy cells. Future studies must carefully map how mitochondrial shape and function align with cancer's multifaceted nature (be it invasion, survival, or resistance) and personalized medicine. Only then can we harness mitochondrial fission not merely as a target, but as a window into cancer's deeper vulnerabilities.

2.4. Mitochondrial fission in fibrosis

Like cancer, abnormal mitochondrial fission is also associated with fibrosis of various organs.[45] In fibrosis, exaggerated fission promotes EMT and the over-accumulation of the extracellular matrix.[159-161]

Mitochondrial fission is well documented in lung fibrosis. Environmental stressors, such as particulate matter (PM) 2.5 and toxins like paraquat, disrupt mitochondrial integrity in type II alveolar cells, reducing membrane potential and increasing DRP1-mediated fission, while suppressing MFN1/2. This leads to oxidative stress, EMT, and fibrosis.[162,163] Promoting mitochondrial fusion alleviates these effects and reduces collagen deposition.[162] Paraquat also triggers mitochondrial damage and oxidative stress, which can be prevented by DRP1 inhibitors (e.g., Mdivi-1) and antioxidants like N-acetylcysteine.[163] Protective agents, such as microRNA-30a, prevent apoptosis by inhibiting DRP1-dependent fission,[164] while astaxanthin promotes myofibroblast apoptosis through DRP1-mediated fission.[165]

In renal fibrosis, mitochondrial dysfunction and oxidative stress drive disease progression. Excessive fission reduces ATP, elevates ROS, and activates fibroblasts, resulting in collagen deposition.[166] Hyperuricemic kidneys show improved function with autophagy inhibition and reduced *DRP1* expression. Histone-lysine N-methyltransferase regulates *DRP1*-mediated fission and EMT in chronic renal allograft fibrosis.[167] Oxalate-induced fission in renal epithelial cells is mitigated by resveratrol and caffeine.[168] In diabetic kidney disease, enhanced fission correlates with fibrosis,[169] while alpha lipoamide improves mitochondrial function and retinoid X receptor alpha modulation.[170] DRP1 deficiency enhances mitochondrial fitness and prevents diabetic nephropathy,[171,172] with peroxisome proliferator-activated receptor gamma coactivator-1 alpha

(PGC-1α) suppressing DRP1 remodeling and ROS in kidney disease.[173] In acute kidney injury, DRP1 deficiency promotes recovery through enhanced fusion.[174]

Mitochondrial dysfunction, often due to oxidative stress and altered dynamics, plays a key role in liver fibrosis. Low expression of PGC-1α, a master transcriptional coactivator orchestrating mitochondrial biogenesis and respiration, and involved in various metabolic processes, has implications in several diseases.[175,176] This low expression is responsible for the disturbance in mitochondrial dynamics, facilitating hepatocyte EMT and liver fibrosis. Reduced PGC-1α expression impairs mitochondrial biogenesis and promotes hepatocyte EMT and fibrosis. Carbon tetrachloride-induced liver fibrosis is exacerbated in *Pgc1*α knockout mice, but mitigated by ROS scavengers.[7,17] In cholestasis, glycochenodeoxycholate induces mitochondrial fragmentation and ROS, which can be prevented by inhibiting fission.[178,179] Cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction also enhances mitochondrial fission, suggesting potential for targeting CFTR to restore mitochondrial homeostasis in cystic fibrosis-related liver injury.[180,181]

Emerging data strongly support the role of mitochondrial fission in perpetuating fibrotic processes across multiple organs. However, the precise context-specific mechanisms—such as how tissue-specific microenvironments, fibrogenic signals, or metabolic cues modulate DRP1 activity—remain insufficiently characterized. A comparative understanding of fission regulation in pulmonary, renal, and hepatic fibrosis could uncover shared mitochondrial signatures of fibrogenesis. Moreover, the intersection of fibrosis with pre-neoplastic transformation suggests that sustained mitochondrial fragmentation may not only drive fibrotic pathology but also prime tissues for oncogenic conversion. Thus, targeting mitochondrial fission may serve a dual purpose—inhibiting fibrosis and reducing cancer risk in chronically injured tissues.

3. Mitochondrial fusion

Mitochondrial fusion is essential for preserving mitochondrial function by enabling the exchange of mtDNA, proteins, and metabolites between mitochondria, ensuring uniform distribution of bioenergetic capacity and mitigating the effects of mitochondrial damage.[42,61,182] The dynamic regulation of mitochondrial fusion allows cells to adapt to metabolic demands, oxidative stress, and developmental cues.[183-185] In contrast, defects in fusion contribute to a wide range of diseases, including neurodegenerative disorders, metabolic syndromes, and cardiovascular pathologies.[80,186-188]

The mitochondrial fusion process occurs in two sequential steps: the initial fusion of the OMM, followed by the merging of the IMM. These events are mediated by a set of highly conserved GTPases, primarily MFN1 and MFN2 for OMM fusion, and optic atrophy (OPA) 1 for IMM fusion.[189,190] The interplay between these proteins ensures the proper regulation of mitochondrial architecture, facilitating optimal bioenergetic function and resistance to cellular stress.

3.1. Molecular mechanisms of mitochondrial fusion

3.1.1. Outer membrane fusion: role of mitofusins

The fusion of the OMM is orchestrated by the MFN proteins, MFN1 and MFN2, which are homologous GTPases embedded in the mitochondrial outer membrane. These proteins share a similar structure, consisting of an N-terminal GTPase domain, two transmembrane domains, and a heptad repeat (HR) domain.[189,191] The HR domains mediate homotypic and heterotypic interactions between MFNs on adjacent mitochondria, forming trans-oligomeric complexes that tether mitochondrial membranes together.[192,193] The hydrolysis of GTP by MFN1 and MFN2 generates conformational changes that bring the OMMs into proximity, enabling lipid bilayer merging and initiating mitochondrial fusion.[59,194,195]

Although MFN1 and MFN2 share structural similarities, they have distinct functional roles. MFN1 exhibits higher GTPase activity and is more efficient at promoting membrane fusion, whereas MFN2 plays a critical role in linking mitochondria to the endoplasmic reticulum and regulating calcium signaling.[195] In addition, MFN2 is subjected to regulation by the ubiquitin-proteasome system through Parkin-mediated ubiquitination, linking mitochondrial fusion to mitophagy.[196,197] This degradation pathway ensures the selective removal of damaged mitochondria, highlighting the intricate balance between mitochondrial fusion and quality control.

3.1.2. Inner membrane fusion: function of OPA1

Once the OMMs have fused, the fusion of the IMM is mediated by OPA1, a dynamin-related GTPase localized to the IMM. OPA1 is synthesized as a long isoform (L-OPA1), which is anchored to the IMM and is further processed into a short isoform (S-OPA1) by the proteases OMA1 zinc metallopeptidase and YME1-like 1 ATPase.[198] The balance between L-OPA1 and S-OPA1 is critical for IMM fusion and cristae remodeling, with L-OPA1 actively promoting fusion and S-Opa1 regulating mitochondrial structure under stress conditions.[199] Emerging evidence suggests that cardiolipin, a mitochondria-specific phospholipid, plays a crucial role in modulating OPA1 activity and IMM fusion.

Cardiolipin directly interacts with OPA1 to stabilize its function, and alterations in cardiolipin composition can disrupt mitochondrial dynamics, leading to bioenergetic deficiencies.[200] The importance of OPA1 in maintaining mitochondrial function is underscored by its association with autosomal dominant OPA, a neurodegenerative disorder characterized by progressive retinal ganglion cell degeneration and vision loss.[201]

3.2. Regulatory mechanisms of mitochondrial fusion

Mitochondrial fusion is tightly regulated by a variety of PTMs, which fine-tune the activity of fusion proteins in response to cellular signals such as metabolic stress, oxidative damage, and changes in energy demand.[62] Phosphorylation, acetylation, and ubiquitination are key PTMs that modulate the stability, localization, and activity of MFNs and Opa1, ensuring the dynamic control of mitochondrial networks.

Transcriptional coactivators such as PGC-1β and PGC-1α positively regulate and enhance fusion by increasing the expression of MFN2 and interacting with nuclear receptors like estrogen-related receptor alpha, particularly in metabolically active tissues.[202-204] Acetylation of MFN1 reduces its GTPase activity, while deacetylation by protein such as histone deacetylase 6 enhances its function under conditions of glucose deprivation, promoting mitochondrial fusion.[205] Phosphorylation of *MFN1* at threonine 562 by the MEK/ERK signaling pathway inhibits its fusion activity and promotes interactions with pro-apoptotic proteins such as BAK, linking mitochondrial dynamics to apoptosis.[206] Conversely, stress-induced phosphorylation of *MFN2* by JNK and PTEN-induced kinase 1 (PINK1) targets it for proteasomal degradation, tipping the balance toward fission and proliferation in disease contexts.[207,208] PINK1 phosphorylation sites on *MFN2* serve as docking signals for Parkin, facilitating mitophagy and quality control.[192,209] Regulatory E3 ubiquitin ligases, such as MARCH5, mediate ubiquitination and degradation of MFNs, adjusting fusion capacity in response to proteostatic demands.[103,210] Additional layers of control arise from SUMOylation pathways, ER-mitochondria tethering,[211] and novel regulators such as MTFP1, which coordinates inner membrane integrity and mtDNA maintenance through fusion-dependent mechanisms.[59] Recent findings further implicate the dual regulation of mitochondrial fusion by the Parkin-PINK1 axis and OMA1-dependent proteolysis, controling fusion at both mitochondrial membranes.[212] Together, these findings reveal mitochondrial fusion as a convergence point of metabolic signaling, stress responses, and organelle quality control.

3.3. Mitochondrial fusion in cancer

Mitochondrial fusion has a multifaceted and context-dependent function in cancer, affecting metabolic plasticity, resistance to apoptosis, and tumor growth. While in certain cancers, mitochondrial fusion inhibits tumorigenesis through the preservation of mitochondrial integrity and control of cellular signaling pathways, in others, mitochondrial fusion enhances malignancy through metabolic adaptation and improved survival. This duality of mitochondrial fusion highlights the necessity for cancer type-specific research.

3.3.1. Tumor-suppressive function of mitochondrial fusion

In multiple cancers, mitochondrial fusion inhibits tumorigenesis by regulating metabolism and suppressing EMT. In ovarian cancer, overexpression of *MFN2* promotes autophagy, inhibits ROS production through the adenosine monophosphate-activated protein kinase/mTOR/ERK pathway, and ultimately blocks cell growth, invasion, migration, and EMT, and is associated with enhanced patient survival.[213] Likewise, in bladder cancer, downregulation of *MFN2* correlates with more aggressive tumors, and decreased expression with advanced stage, increased grade, and lymph node metastasis. Mechanistically, it is indicated that MFN2 functions as a tumor suppressor in bladder cancer by suppressing the Wnt/β-catenin signaling pathway.[214]

In pancreatic cancer, the promotion of mitochondrial fusion through upregulation of *MFN1* and *MFN2* makes cancer cells metabolically rigid and vulnerable to metabolic stress and apoptosis.[215] In thyroid cancer, altered mitochondrial metabolism, impaired OXPHOS, enhanced glycolysis, and dysregulated mitochondrial dynamics contribute to tumor progression and therapeutic resistance.[216] In addition, *MFN2*, which is highly downregulated in thyroid cancer, controls EMT through the AKT pathway. Knockdown of *Mfn2* promotes migration and invasion, while overexpression inhibits these cancerous traits.[217]

In HCC, *MFN1*, a key mediator of mitochondrial fusion, is typically downregulated, causing mitochondrial fragmentation and EMT activation. This mechanism promotes tumor invasion, suggesting that the restoration of *MFN1* function may be a therapeutic strategy.[218] Likewise, in colorectal cancer, protein tyrosine phosphatase-like A domain containing 1, a mitochondrial dynamics regulator, inhibits metastasis by stabilizing mitochondrial structure and inhibiting EMT through rapidly accelerated fibrosarcoma/ERK signaling.[219]

Mitochondrial dynamics also play an important role in breast cancer development. The flavonoid silibinin has been

reported to suppress the migration and invasion of breast cancer cells by inducing mitochondrial fusion through increasing MFN1, MFN2, and OPA1 levels and reducing DRP1 levels to inhibit EMT.[220] Furthermore, estrogen receptor beta (ERβ) is also responsible for maintaining mitochondrial network integrity and blocking EMT under obesity-induced inflammation in breast cancer. This is achieved through enhanced mitochondrial fusion and biogenesis, along with attenuated oxidative stress and invasiveness. Elevated ERβ levels are associated with elevated epithelial marker levels and reduced mesenchymal marker levels, effectively inhibiting metastasis.[221]

The tumor suppressor p53 directly controls *MFN2* by binding to its promoter, linking the control of mitochondrial dynamics to p53-mediated tumor suppression.[222] p53 plays a crucial role in maintaining mitochondrial integrity, promoting apoptosis, and inhibiting tumor progression. This suggests that Mfn2 may contribute to tumor suppression in a p53-dependent manner by stabilizing mitochondrial structure and preventing metabolic reprogramming that favors tumor growth. However, in cancers where p53 is mutated or inactivated, MFN2 may lose its tumor-suppressive role, leading to tumor progression in certain contexts. The relationship between mitochondrial fusion and cancer is depicted in Figure 5.

3.3.2. Oncogenic role of mitochondrial fusion

Although it acts as a tumor suppressor in most cancers, MFN2 has oncogenic functions in some cancers. High expression of *MFN2* in cervical cancer is associated with an unfavorable prognosis. Knockdown of *Mfn2* in cervical cancer cell lines (SiHa and HeLa) results in reduced proliferation, migration, invasion, and colony formation, suggesting that MFN2 facilitates tumorigenesis through the induction of EMT and activation of the Wnt/β-catenin pathway.[223,224]

In most cancers, fusion maintains healthy mitochondria, optimizes correct energy production, inhibits EMT, and controls tumor growth. However, in certain cancers, such as cervical cancer, the same fusion machinery appears to promote tumor development by ensuring that cancer cells survive, migrate, and invade. This dual behavior highlights that mitochondria are not simply inert powerhouses; they are dynamic, and cancer cells can manipulate these processes for their benefit. Future studies must carefully examine when fusion is protective against cancer and when it drives cancer progression, taking into account variables such as tissue type, genetic mutations (e.g., p53 status), and the tumor microenvironment. Such clarity is essential before targeting mitochondrial fusion as a cancer therapy. Without this insight, interventions could have unintended consequences. Future therapies can be tailored to match the particular mitochondrial behavior of a given cancer, turning this complexity into an advantage.

3.4. Mitochondrial fusion during fibrosis

Mitochondrial fusion is a tightly regulated process influenced by metabolic stress, oxidative stress, calcium homeostasis, and cell cycle phases.[182] Dysregulation of this process has been implicated in the progression of several fibrotic diseases.

In pulmonary fibrosis, exposure to PM2.5 disrupts mitochondrial dynamics by downregulating fusion proteins MFN1/2 and upregulating DRP1, enhancing fragmentation and promoting EMT.[162] Restoration of fusion reverses these fibrotic effects. In retinal fibrosis, TGF-β suppresses OPA3, a mitochondrial fusion regulator, inducing elongation and increasing mesenchymal markers such as N-cadherin and vimentin in RPE cells, where blocking TGF-β signaling prevents these changes.[225,226] In chronic kidney disease, pioglitazone restores mitochondrial homeostasis by enhancing fusion (through OPA1, MFN2) and reducing DRP1-mediated fission, lowering ROS levels and fibrosis.[227] Fusion proteins also maintain lipid metabolism in alveolar type II cells, and their deficiency leads to surfactant dysfunction and progressive lung fibrosis.[228] SIRT3, a mitochondrial deacetylase, promotes fusion and reduces inflammation in renal fibrosis models; its activation by honokiol ameliorates oxidative stress and fibrosis following unilateral ureteral obstruction.[229] In liver fibrosis, activated hepatic stellate cells display enhanced mitochondrial fusion, glycolysis, and OXPHOS, underscoring a metabolic–mitochondrial axis in fibrogenesis.[230] Together, these findings illustrate how impaired mitochondrial fusion contributes to fibrotic progression, and how its restoration may serve as a viable therapeutic strategy across various organs.

4. Interplay between fusion and fission

The regulation of mitochondrial dynamics involves the synergistic yet opposing mechanisms of fission and fusion, whose joint modulation determines mitochondrial structure, location, energy generation, and quality control.[19,61,231] In numerous physiological and pathological conditions – such as fibrosis and cancer – it is the breakdown of this dynamic balance, rather than the autonomous initiation of either process, that is central to cell dysfunction and disease.[80,232,233] Initial yeast genetic studies highlighted the opposing activities of DNM1P (a dynamin-related GTPase that mediates fission) and FZO1P (an outer membrane fusion protein), establishing that mitochondrial shape is controlled by the close interplay between these two opposing forces.[234,235] These findings

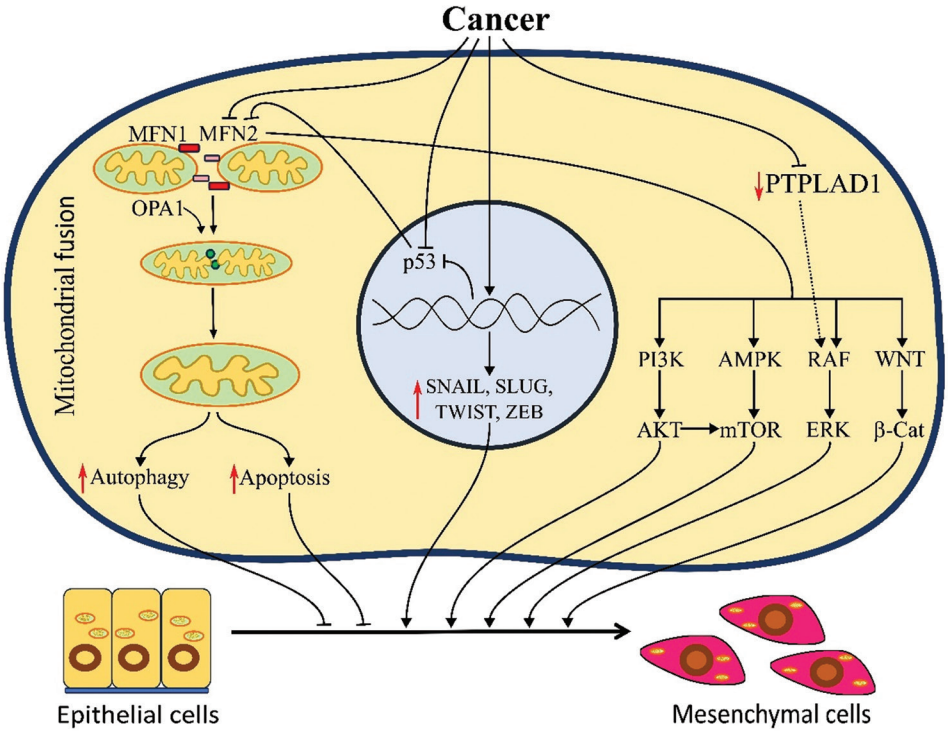

Figure 5. Association of mitochondrial fusion in cancer and epithelial-mesenchymal transition (EMT). Mitochondrial fusion regulates metabolism and suppresses EMT by increasing autophagy and apoptosis. Cancer downregulates protein tyrosine phosphatase-like A domain containing 1 (PTPLAD1), which activates rapidly accelerated fibrosarcoma (RAF)/extracellular signal-regulated kinase (ERK) axis and induces EMT. Cancer cells also downregulates tumor suppressor protein (p53) and mitofusin (MFN) 2, and the suppression of the latter activates phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), adenosine monophosphate-activated protein kinase (AMPK)-mTOR, and Wnt/β-catenin (β-cat) pathways, as well as transcription factors that collectively promote mesenchymal phenotypes. Image created by authors using Inkscape drawing software. Abbreviation: OPA1: Optic atrophy 1.

have since been applied to mammalian systems, where DRP1 (homolog of DNM1P), MFN1, MFN2 (homolog of FZO1P), and OPA1 control fission and fusion events.[43,62] However, it is not merely the increase in fission or fusion but the disordered balance between the two that drives pathological mitochondrial phenotypes.

In fibrotic disease, the equilibrium shifts toward the fission direction. Activated fibroblasts in fibrosis also contain fragmented mitochondria due to the upregulation of DRP1 and the inhibition of fusion-linked proteins such as MFN1/2.[162] Such changes diminish oxidative capacity and augment ROS generation, which facilitates fibroblast activation and extracellular matrix deposition.[236] While mitochondrial fragmentation underlies these phenotypes, the loss of the ability to fuse is also central to preserving dysfunction. Hence, in cancer as well, mitochondrial dynamics are leveraged to facilitate metabolic reprogramming and tumor development. DRP1-mediated fission enables mitochondrial fragmentation, which supports the glycolytic condition typical of numerous tumors (i.e., the Warburg effect) and promotes proliferation and cell division.[113,127,132] However, mitochondrial fusion is not eliminated; rather, it is selectively re-recruited during stress conditions such as drug therapy or hypoxia to preserve mitochondrial integrity, prevent apoptosis, and ensure survival.[80,237] This explains the dynamic switching between fission and fusion based on metabolic demands or environmental stress in cancer cells. Interestingly, the cooperative interaction between fission and fusion is required to control mitophagy and other quality control mechanisms for mitochondrial integrity.[238,239] Fission acts to eliminate impaired mitochondrial fragments by separating and degrading them through autophagy, while fusion allows mitochondrial defects to be repaired and diluted.[240-242] Disruption of this collaborative process results in the accumulation of defective mitochondria, decreased mitophagy, and increased oxidative stress – all factors typically observed in both fibrosis and tumorigenesis.[237] Given this complexity, therapeutic strategies targeting mitochondrial dynamics must transcend simple inhibition of fission or enhancement of fusion. Instead, these strategies should focus on restoring the normal physiological balance between the two processes. Pharmacological agents, such

as DRP1 inhibitors (e.g., Mdivi-1) and MFN2 stabilizers, show promise in preclinical models, offering the potential to rebalance mitochondrial dynamics and reduce disease phenotypes without driving the system toward excessive fusion or fission.[78]

The dynamic equilibrium between mitochondrial fission and fusion is not a fixed characteristic but a responsive, context-sensitive process regulated by cell stress and metabolic status. In cancer and fibrosis, failure of this equilibrium represents a maladaptive effort to maintain survival at the expense of mitochondrial function, resulting in fragmentation, oxidative stress, and defective quality control. This perspective suggests that successful therapies must aim to rectify, rather than circumvent, mitochondrial dynamics. Rather than focusing on fission or fusion independently, we need to address the broader regulatory environment that sustains mitochondrial homeostasis, providing a more subtle and possibly long-lasting avenue for intervention.

5. Mitochondrial dynamics and mitochondrial stress response

Cells are constantly exposed to various stressors, including excessive ROS, calcium dysregulation, misfolded proteins, and mtDNA damage, all of which destabilize membrane potential and disrupt metabolic function.[243-246] To counteract these stressors, cells activate protective responses, such as the mitochondrial unfolded protein response and the integrated stress response, which reduce proteotoxic stress by inducing chaperone expression, promoting protein degradation, and adjusting cytosolic translation. These pathways are critical for mitochondrial proteostasis and metabolic adaptation; however, they are somewhat beyond the main focus of this review.[247-251] To restore homeostasis, cells also initiate a coordinated mitochondrial quality control system, which includes fission, fusion, biogenesis, and, importantly, mitophagy.[54,252] Fission facilitates the segregation of damaged mitochondrial components, which are subsequently removed through mitophagy, a selective form of autophagy mediated by the PINK1–Parkin pathway. This process prevents the accumulation of dysfunctional organelles that could otherwise trigger excessive ROS production, disrupt cell metabolism, or activate apoptotic signaling. In addition, alternative receptor-mediated mitophagy pathways, governed by proteins such as BCL2/adenovirus E1B 19 kDa protein-interacting protein 3, NIX, and FUN14 domain-containing protein 1, are particularly active under conditions such as hypoxia or erythroid maturation.[75,252-254] These receptor pathways enable mitophagy independent of ubiquitination, broadening the impact of mitophagy beyond a single mechanism. Mitophagy is not merely a mitochondrial waste disposal mechanism; rather, it plays a critical role in determining cell fate and function, being crucial for maintaining mitochondrial health and energy homeostasis. Importantly, failure or dysregulation of mitophagy is increasingly linked to the pathogenesis of neurodegenerative diseases, cardiovascular dysfunction, cancer, and aging, underscoring its therapeutic potential.[54,252] Concurrently, fusion allows for the mixing of mitochondrial contents, diluting damage and maintaining functional complementation. To restore lost organelles and support recovery, mitochondrial biogenesis, regulated by transcriptional coactivators such as PGC-1α/β and nuclear respiratory factors, generates new mitochondria, restoring network capacity and metabolic competence.[255-258] Together, these adaptive mechanisms dynamically reshape the mitochondrial network, sustain cellular energy homeostasis, and determine survival under stress.

In cancer, this system becomes a tool for survival. Tumor cells exploit mitochondrial stress responses and dynamics to adapt to hostile environments, evade cell death, and support processes like EMT, which are crucial for metastasis. Understanding this interplay could reveal vulnerabilities that might be exploited to impair cancer cell resilience or prevent fibrosis, as it supports pathological features such as invasiveness, resistance to apoptosis, and tissue remodeling. These features are hallmarks of cancer and fibrosis, making mitochondrial quality control a promising therapeutic target in both diseases.

6. Mitochondrial dynamics and medicine

Mitochondrial dynamics play a crucial role in cellular homeostasis, with their dysregulation implicated in diseases such as cancer, fibrosis, and neurodegeneration. Targeting mitochondrial fission and fusion proteins offers a promising therapeutic strategy. The main targets of modulating mitochondrial dynamics are DRP1, a central regulator of mitochondrial fission, and the fusion proteins MFN1, MFN2, and OPA1. Pharmacological modulation of these proteins – particularly with natural and synthetic compounds – may provide immense therapeutic potential.

Rutin, a natural product flavonoid, suppresses DRP1-mediated fission and confers protection against ethanol-induced hepatotoxicity in HepG2 cells and zebrafish models.[259] Similarly, isoliquiritigenin suppresses glutamate-evoked mitochondrial fission in hippocampal neurons through calcineurin-dependent dephosphorylation of *DRP1*, with a focus on its neuroprotective effect and might be used for antifibrotic, and anticancer activities.[260] Curcumin, a compound found in turmeric, is highly acclaimed for its anticancer,[261,262] anti-inflammatory,[263-265] and antifibrotic

activities. Curcumin regulates mitochondrial proteins, which enhance mitochondrial function in silicosis[266] and acute kidney injury,[267] and helps regulate mitochondrial dynamics in diseases related to EMT. In cisplatin-induced acute kidney injury, curcumin decreases mitochondrial fission 1 protein levels and restores OPA1 protein levels, thereby maintaining mitochondrial dynamics and protecting against mitochondrial dysfunction.[268] In addition, curcumin prevents mitochondrial fission disturbances in early nephrectomy by promoting fusion through upregulation of OPA1 and MFN1 and decreasing fission, which is linked to reduced oxidative stress and preserved mitochondrial bioenergetics.[269] Flavanones, such as naringenin and hesperetin, also inhibit DRP1-mediated fission, leading to mitochondrial fusion, disruption of cancer cell metabolism, and apoptosis in multiple myeloma cells.[270] Likewise, triterpenoid hederagenin, which has shown anticancer, anti-inflammatory, and antifibrotic potential,[271] inhibits mitochondrial fission in ovarian cancer cells through DRP1inhibition, disrupting energy metabolism, and triggering apoptosis.[272]

Quercetin has inhibitory activity against DRP1 activity, conferring a protective effect against ischemic and metabolic disease.[273,274] Baicalein suppresses cardiac damage and acute lung injury by suppressing DRP1,[275,276] while mangiferin inhibits DRP1 and mitophagy proteins, providing a protective role in neuronal disorders.[277] Silibinin, a milk thistle flavonolignan, also induces mitochondrial fusion, which subsequently suppresses the migration and invasion of breast cancer cells.[220]

Resveratrol improves mitochondrial health through upregulation of MFN2, OPA1, and FIS, maintaining the fusion and fission processes and preserving mitochondrial integrity in neuronal models.[278] Moreover, other natural and bioactive compounds have shown promising therapeutic potential by modulating mitochondrial dynamics, especially through the inhibition of DRP1-mediated fission, offering protection in neurodegenerative and metabolic disorders.[279,280] By restoring mitochondrial homeostasis and reducing oxidative stress, these compounds present a novel strategy for targeting mitochondrial dysfunction.[279] In addition to naturally occurring molecules, some synthetic agents are emerging as significant regulators of mitochondrial dynamics. The molecule 15-oxospiramilactone enhances *MFN1* and *MFN2* activation by suppressing the deubiquitinase USP30, which, in turn, enhances mitochondrial fusion and cellular welfare.[281] A study by Zacharioudakis *et al.*[282] recognized that certain chemical activators maintain MFNs in an open, fusion-capable conformation, thereby increasing mitochondrial function and cell survival on stressful conditions.

Mitochondrial fission is also implicated in the pathogenesis of metabolic diseases. Melatonin can suppress DRP1-mediated fission in diabetic animal hearts through the SIRT1-PGC-1α pathway, thereby conferring protection against diabetic cardiomyopathy and improving mitochondrial function.[283] Among synthetic fission inhibitors, the most studied is Mdivi-1. It is a selective DRP1 inhibitor that inhibits mitochondrial fission, causing elongation in thyroid cancer cells, and inhibits proliferation and EMT by blocking the NF-κB pathway.[216] Mdivi-1 also inhibits mtDNA-mediated inflammation and oxidative stress in pulmonary fibrosis models,[163] and it maintains mitochondrial structure and integrity by inhibiting DRP1 activity.[156] It is currently being investigated for its therapeutic potential in cancer, neurodegeneration, and fibrosis.

Drug repurposing or repositioning offers a vast library of compounds that can be evaluated for their potential to regulate mitochondrial processes.[284] Moreover, *in vivo*, *in vitro*, and *in silico* platforms[285-287] are available, which can be utilized to expedite the selection of drugs for further testing *in vivo* or *in vitro*. Several microRNAs and other non-coding RNAs have also been shown potential in regulating either EMT or mitochondrial dynamics,[288-291] although several other non-coding RNAs require further evaluation.

Recent findings suggest that antifibrotic therapies may offer unexpected benefits beyond fibrosis management, extending into cancer treatment. Pirfenidone, an antifibrotic agent used for IPF, not only attenuates fibrosis by modulating TGF-β signaling and activating peroxisome proliferator-activated receptor gamma pathways but also alters NF-κB activity, potentially reducing HCC risk.[292] Clinical trials have shown that perioperative use of pirfenidone may lower the risk of acute exacerbation in IPF patients undergoing lung cancer surgery, ensuring safer surgical outcomes.[293,294] In addition, it is being tested to prevent radiation-induced lung injury in esophageal cancer patients,[295] and epidemiological data suggest it might decrease lung cancer incidence in IPF populations.[296] Another antifibrotic drug, nintedanib, a multi-kinase inhibitor, has demonstrated improved chemotherapy efficacy in non-small cell lung cancer patients with comorbid IPF.[297] New molecular targets, such as the microRNA-143/-145 cluster and galectin-3, are also being explored to enhance tumor responsiveness to therapy and disrupt pro-fibrotic tumor environments.[298,299] Together, these findings represent a promising convergence of antifibrotic and anticancer strategies, potentially enabling dual-purpose interventions that could the manage both fibrosis and cancer. Further research is required to define

the molecular basis for such processes and the clinical use of these novel treatments to optimize disease therapy and mitochondrial health.

Although these drugs have shown promising results in preclinical models, their clinical translation requires a more comprehensive understanding of their specificity, bioavailability, and long-term safety. The context-dependent roles of mitochondrial fission and fusion in the pathogenesis of disease further complicate the development of broadly applicable therapeutics, underscoring the need for precision medicine approaches. Combining high-throughput screening, drug repurposing pipelines, and multi-omics technologies could potentially accelerate the discovery of novel regulators and biomarkers of mitochondrial dysfunction. Moreover, the emerging role of non-coding RNAs, including microRNAs and long non-coding RNAs, as upstream regulators of both mitochondrial dynamics and EMT presents a promising, though underexplored, therapeutic avenue. Ultimately, realizing the full potential of targeting mitochondrial dynamics in complex diseases will require coordinated efforts spanning basic research, drug development, and clinical translation.

Understanding the role of mitochondrial dynamics in EMT requires an integrative, multidimensional approach that goes beyond isolated experiments. Single-cell omics can reveal how individual cells differ in their mitochondrial changes during EMT, providing insights into partial or hybrid EMT states. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9-based genetic screens may uncover previously unknown regulators that link EMT and mitochondrial dynamics, offering new therapeutic targets. Real-time live-cell imaging can track mitochondrial remodeling in terms of morphology, distribution, and function, providing further clarity on the mitochondrial changes during EMT. Such observations can also be performed *in vivo* to analyze the complexity of tissue and microenvironmental influences. Developing mitochondrial-targeted therapeutics designed to specifically act on EMT-activated cells, while preserving overall mitochondrial function, is essential for maintaining tissue homeostasis. Computational modeling, systems biology and network analysis can further elucidate how cells change behavior and uncover new opportunities for research and therapeutic interventions. In addition, the analysis of patient-derived tissues for gene expression and large-scale genomic data sets can validate these findings and assess their potential in therapeutic applications. These experimental, computational, and translational efforts will help build a comprehensive understanding of mitochondrial dynamics and EMT.

7. Conclusion

Mitochondrial dynamics, comprising fusion and fission processes, play a pivotal role in EMT and significantly influence the development of key diseases such as cancer and fibrosis. While efforts have been made to establish the link between EMT and mitochondrial dynamics in cancer metastasis, the field remains relatively porous across different stages and types of cancer. Challenges such as drug specificity, bioavailability, and safety continue to limit clinical translation of these findings. Future studies employing multi-omics, CRISPR-based screens, and advanced imaging technologies will be essential to uncover novel targets and refine therapeutic strategies, paving the way for precision interventions that modulate mitochondrial dynamics in disease. The convergent involvement of EMT in both fibrosis and cancer metastasis suggests the potential of antifibrotic therapy for preventing the advanced stages of various cancers.

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The authors declare that they have no competing interests.

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