



Review Article

Mitochondrial Dynamics in Breast Cancer Metastasis: From Metabolic Drivers to Therapeutic Targets



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Abstract

Mitochondria are highly dynamic organelles that adapt to cellular stress and metabolic demands through processes such as fission, fusion, mitophagy, and transport, all of which are vital for maintaining cellular signaling and metabolic homeostasis. Fission facilitates mitochondrial division and biogenesis, while fusion enhances mitochondrial fitness and metabolic flexibility by mitigating damage. Together, these processes play a critical role in regulating cellular stress responses and apoptosis. Dysregulation of mitochondrial dynamics has been linked to impaired development and cancer progression, including breast cancer metastasis. A comprehensive understanding of mitochondrial dynamics in breast cancer progression is essential for advancing precision medicine. This review delves into the intricate molecular mechanisms governing mitochondrial biogenesis, fission, fusion, and mitophagy, with a particular focus on the role of mitophagy in maintaining mitochondrial homeostasis and its connection to metastasis progression. Furthermore, it discusses potential therapeutic strategies targeting mitochondrial dynamics and highlights the critical steps necessary to translate these approaches into clinical trials.

Introduction

Metabolic reprogramming is a well-established hallmark of cancer, enabling cancer cells to adapt, survive, and proliferate under environmental constraints.^{1–3} This process is highly dynamic, resulting in distinct metabolic characteristics across different tumors, where cancer and stromal cells exhibit metabolic diversity.^{4,5} Originally described by Otto Warburg, tumor cells were thought to rely predominantly on aerobic glycolysis—known as the Warburg effect—for rapid growth and proliferation, attributed to presumed mitochondrial dysfunction.⁶ However, subsequent research has revealed that mitochondrial oxidation also plays a crucial role in supporting the metabolic demands of rapidly progressing cancers.^{6–8} Unlike normal cells, cancer cells frequently disrupt tightly regulated metabolic pathways, leading to the deregulation of signaling cascades. These alterations enable cancer cells to meet their elevated energy demands and support anabolic processes essential for tumor growth and survival.^{9,10} An emerging concept is that the

tumor microenvironment imposes selective pressures that drive cancer cell evolution, ultimately promoting metastasis and drug resistance. This is particularly evident in triple-negative breast cancer (TNBC), which requires a high adenosine triphosphate (ATP) supply to sustain its rapid growth and proliferation.^{11–13} Metabolic rewiring is increasingly recognized as a key driver of breast cancer progression, as cancer cells adapt to fluctuations in energy demand and supply—a concept referred to as bioenergetic efficiency (BE).^{14,15}

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide. TNBC, which accounts for approximately 15–20% of all breast cancer cases, is associated with a higher recurrence rate and poorer survival outcomes compared to non-TNBC.^{16,17} This aggressive subtype is characterized by the absence of three key receptors: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. The lack of these therapeutic targets makes metastatic TNBC particularly challenging to treat, resulting in high fatality rates.^{18,19} Metabolic adaptations play a critical role in TNBC progression, with elevated lipolysis and fatty acid oxidation (FAO) compensating for high energy demands during rapid proliferation, even under hypoxic conditions.^{20,21} Metastatic cancer cells undergo extensive metabolic reprogramming, including increased fatty acid transport, lipid droplet accumulation, de novo lipogenesis, and β -oxidation, to meet their heightened ATP requirements. While glycolysis was once considered the predominant pathway driving cancer progression, subsequent findings have highlighted

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the direct involvement of mitochondrial metabolism in facilitating rapid tumor growth.^{22,23} Interestingly, mitochondrial bioenergetics and FAO have been shown to play pivotal roles in maintaining cancer stemness, supporting survival and proliferation, and driving chemoresistance in TNBC.^{24,25} This growing understanding underscores the importance of targeting metabolic pathways as a potential therapeutic strategy for aggressive breast cancer subtypes.^{26–28} Maintenance of BE is critical for metastatic cancer growth. BE is defined as the amount of ATP produced per molecule of nutrient metabolized in the mitochondria, while mitochondrial ATP synthesis capacity refers to the rate of ATP generation per unit of time.^{29,30} However, mitochondrial adaptation extends beyond BE, involving changes in mitochondrial architecture and adjustments to nutrient availability.³¹ In this context, TNBC preferentially utilizes readily available fatty acids as a primary energy source to meet its extensive energy demands required for rapid growth and survival.³² This is achieved through the strategic hijacking of mitochondrial bioenergetics machinery, enabling TNBC cells to sustain their high metabolic requirements.^{33,34} Mitochondria, widely regarded as central hubs of cellular metabolism, play a pivotal dual role in supporting the energetic and biosynthetic demands of oncogenesis. Their functions extend to facilitating malignant transformation, driving tumor progression, and influencing anticancer immunosurveillance mechanisms.^{35,36} Moreover, mitochondria support uncontrolled proliferation, drive tumor advancement, and enable anaplerotic processes that are vital for sustaining cancer cell metabolism under diverse and challenging environmental conditions.^{37,38}

Mitochondrial dynamics encompass the processes of movement, tethering, fusion, and fission that collectively shape mitochondrial architecture.³⁹ Increasing evidence highlights the critical role of mitochondrial dynamics in maintaining cell viability, preventing senescence, ensuring mitochondrial health, supporting bioenergetic function, regulating quality control, and mediating intracellular signaling.^{40,41} These dynamics are intricately linked to the balance between energy demand and ATP synthesis capacity, with mitochondrial architecture adapting in response to shifting metabolic needs. Transient shifts between interconnected and fragmented states reorganize mitochondrial components and remove damaged material through coordinated mitophagy, fission, and fusion, maintaining a healthy mitochondrial population.^{42,43} However, the dual demands of bioenergetic adaptation and quality control may conflict under specific nutrient conditions. Nutrient availability and metabolites can drive structural changes in mitochondria as an adaptive response to fluctuating ATP demands.^{44,45} This dynamic remodeling represents a potential therapeutic target, particularly in aggressive cancers, where disrupting the interplay between mitochondrial bioenergetics and architecture could impair the metabolic flexibility essential for tumor survival and proliferation.^{46,47}

This review provides a comprehensive analysis of the critical role of mitochondrial dynamics and bioenergetics in driving the rapid progression of cancer cells, with a particular focus on breast cancer. It explores how these processes contribute to breast cancer metastasis and highlights their potential as therapeutic targets. The discussion spans the full spectrum of mitochondrial bioenergetics and biosynthesis, including biogenesis, turnover, fission, fusion, mitophagy, oxidative stress regulation, metabolism, and ATP synthesis. Furthermore, the review delves into the regulatory mechanisms linking mitochondrial dynamics to cancer progression, emphasizing their significance in identifying therapeutic opportunities. By consolidating current knowledge, it offers valuable

insights into potential drug targets and novel therapeutic strategies to improve breast cancer treatment outcomes.

Mitochondrial metabolism and breast cancer plasticity

Metabolic variations across cancer types provide critical insights into cancer progression.^{48,49} Cellular metabolism differs between low- and high-grade tumors and between primary and metastatic sites.⁵⁰ Recent studies have demonstrated the strong inhibitory effects of elesclomol on diverse cell types, including cancer stem cells, drug-resistant cells, and cells with low glycolytic activity, primarily by targeting and enhancing mitochondrial metabolism.⁵¹ Otto Warburg first identified aerobic glycolysis as a key driver of tumor growth, a concept later expanded in the 1990s with findings linking mitochondrial respiration to metastasis.^{52,53} Despite decades of research, progress in understanding energy metabolism reprogramming—one of cancer's hallmarks—has been limited. While molecular therapies and immunotherapies have taken center stage, recent discoveries linking metabolic reprogramming to immune evasion and drug resistance have renewed interest in targeting cancer metabolism.^{54–56}

Glucose metabolism begins with hexokinase converting glucose into glucose-6-phosphate, ultimately yielding ATP and pyruvate for mitochondrial respiration. Pyruvate enters the citric acid (tricarboxylic acid, TCA) cycle as acetyl-CoA, which fuels oxidative phosphorylation or is converted by ATP citrate lyase into cytoplasmic acetyl-CoA. This acetyl-CoA is essential for FAO and synthesis, with ACC α regulating FAO inhibition via malonyl-CoA production. Citrate serves as a key carbon source for fatty acid and cholesterol synthesis, facilitated by fatty acid synthase (FASN) and supported by NADPH (nicotinamide adenine dinucleotide phosphate) from the pentose phosphate pathway.⁵⁷ Enzymes such as elongases and desaturases further process long-chain fatty acids into complex lipids crucial for membrane biogenesis, protein modification, and cellular signaling in metastasis.^{58,59} Elevated levels of FASN, citrate synthase, and ATP citrate lyase are commonly observed in malignancies, highlighting their role in tumor growth and survival.⁶⁰ This interplay between glycolysis and lipid metabolism reveals promising therapeutic targets in cancer treatment.^{61,62} Cancer metabolic plasticity is believed to drive fatty acid (FA), phospholipid, and lipid synthesis through de novo lipogenesis, promoting tumor growth and survival.⁶³ The tumor-specific antigen OA-519 highlights FASN activity, directly linking FA synthesis to cancer progression.⁶⁴ Enhanced de novo FA synthesis in neoplastic tissues plays a critical role in tumor development, making enzyme targeting a promising therapeutic strategy.^{65,66} Genome-scale metabolic models of breast cancer gene expression underscore the importance of FA biosynthesis in early tumor progression, where anabolic processes dominate, whereas advanced stages rely more on reactive oxygen species (ROS) detoxification.^{67,68} This study offers fresh insights into tumor metabolism, demonstrating that ATP synthesis is lower in primary solid tumors than in normal tissues but increases in metastases.⁶⁹ By quantifying tumor energy generation rates for the first time, these findings challenge the long-standing view of uniformly high tumor metabolism. Significant metabolic shifts occur throughout tumor progression, with significantly reduced TCA cycle flux in five primary tumors compared to their tissues of origin, yet elevated TCA flux in two breast cancer lung metastasis models relative to both advanced primary lesions and healthy lung tissue.^{70,71} Despite increased glycolytic flux, oxidative phosphorylation remains the dominant ATP source, suggesting reduced ATP production in primary tumors

and increased ATP synthesis in metastases.⁷² Recent findings link triple-negative breast cancer's invasiveness to its dominance over normal and immune cell mitochondrial metabolism, a mechanism also associated with therapy resistance. This may explain the elevated TCA flux observed in metastases.^{73,74}

During breast cancer brain metastasis, breast cancer cells undergoing epithelial–mesenchymal transition show increased glycolysis and lipid metabolism, providing the energy and biosynthetic resources needed for local invasion.⁷⁵ Moreover, cancer cells precisely regulate mitochondrial bioenergetics and dynamics to enhance fatty acid utilization, meeting their elevated energy demands and driving tumor growth. Beyond fatty acid metabolism, this mitochondrial adaptability highlights mitochondrial dynamics as a promising target for cancer therapy, warranting further exploration to fully understand its therapeutic potential.^{76,77}

Mitochondrial fission, fusion, and mitophagy in breast cancer progression

Mitochondria are dynamic, double-membrane-bound organelles vital for cellular functions such as energy production via oxidative phosphorylation.⁷⁸ Their morphology varies by cell type, reflecting specialized roles—fibroblast mitochondria form elongated filaments (1–10 μm long, ~ 700 nm in diameter), while hepatocyte mitochondria are mostly spherical or ovoid.⁷⁹ Constantly remodeled through fission, fusion, and motility, mitochondria adapt to cellular demands. In cultured fibroblasts, rapid fission and fusion enable the complete redistribution of mitochondrial **green fluorescent protein (GFP)** within an hour. The balance between fission and fusion governs mitochondrial morphology across different cell types and conditions.^{80,81} Recent evidence highlights a strong link between cancer progression and disrupted mitochondrial dynamics, which are regulated by the interplay of fission, fusion, and mitophagy processes.^{82–84} Mitochondrial fission, driven by proteins such as dynamin-related protein 1 (Drp1) and mitochondrial fission factor, supports cellular division and growth. In contrast, fusion, mediated by mitofusins (MFN1/2) and optic atrophy 1 (OPA1), maintains mitochondrial integrity and metabolic flexibility.⁸⁵ In metastatic breast cancer, altered phosphorylation and expression of Drp1 play a pivotal role in modulating these dynamics, underscoring their significance in oncogenesis and their potential as therapeutic targets.^{86–88}

Mitochondrial fission is essential for growing and dividing cells, ensuring an adequate mitochondrial population. The GTPase Drp1, critical for mitochondrial fission, is activated via phosphorylation by MAP kinases ERK1/2.⁸⁹ During fission, Drp1 translocates to the outer mitochondrial membrane, binding to receptors such as Fis1, Mff, Mid49, and Mid51 to mediate membrane constriction and division.^{90,91} Mutations impairing Drp1 disrupt fission, causing excessive fusion and elongated mitochondrial tubules.⁹² Recent studies suggest that targeting mitochondrial fission factors can suppress breast cancer proliferation and invasion, offering therapeutic potential.^{93–95} Elevated levels of mitochondrial fission factors, including Drp1, also serve as prognostic markers. Higher Drp1 expression in metastatic cells suggests its upregulation may signal early breast cancer metastasis.^{96,97} Moreover, high Drp1 expression and mitochondrial fragmentation are vital for brain tumor-initiating cells, while Drp1 inhibition via genetic ablation or mDIV1 reduces their tumorigenicity *in vitro* and *in vivo*.⁹⁸ Drp1-dependent fission supports stem cell maintenance in mammary epithelial stem-like cells, enabling the preferential inheritance of newly generated mitochondria during asymmetric

division. This enhances stem-like properties, whereas cells with older mitochondria exhibit reduced growth and differentiation potential.^{99–101} Drp1 inhibition disrupts mitochondrial asymmetry, diminishing stemness and impairing pluripotency reprogramming, emphasizing its role in stem cell biology. Targeting Drp1 to eliminate cancer stem cells offers a promising strategy for achieving lasting cancer cures by addressing tumor recurrence and resistance at its root.^{102–104} Moreover, the Notch pathway plays a pivotal role in breast cancer stem cell metastasis, with high Notch1 messenger RNA expression strongly linked to poor prognosis. Activation of NICD1, the functional domain of the Notch receptor, upregulates the mitochondrial fission factor Drp1, promoting metastasis and presenting therapeutic opportunities.¹⁰⁵ Mitochondrial fission also impacts breast cancer progression through apoptosis and metabolic reprogramming. Since apoptosis is essential for tumor suppression, disrupted fission impairs apoptotic signaling, enabling tumor growth and metastasis. Targeting mitochondrial fission presents a promising strategy for breast cancer therapy.^{106,107}

Mitochondrial fusion, in contrast, involves the merging of the outer and inner membranes of two distinct mitochondria, ensuring the maintenance of a healthy mitochondrial pool through quality control mechanisms. In contrast, mitochondrial fission involves the splitting of a single mitochondrion into two. The dynamic balance of fusion and fission generates interconnected mitochondrial networks that support cellular energy needs and function.¹⁰⁸ Mitochondrial fusion and fission are regulated by key genes, including (1) mitofusins (MFN1, MFN2) for outer membrane fusion, (2) OPA1/mitochondrial genome maintenance 1 for inner membrane fusion, and (3) Drp1/Dnm1 for membrane division. These GTP-hydrolyzing GTPases from the dynamin superfamily are regulated through interactions with binding partners, playing a critical role in both normal and dysfunctional cellular processes.^{109,110} During mitochondrial fusion, MFN1 and MFN2 facilitate outer mitochondrial membrane fusion, while OPA1 mediates inner mitochondrial membrane fusion.¹¹¹ Evidence shows that the M2 subtype of pyruvate kinase (PKM2) binds to MFN2, promoting mitochondrial fusion and oxidative phosphorylation while reducing glycolysis in cancer cells. This metabolic shift inhibits cancer cell proliferation and metastasis.¹¹² mTOR, a serine/threonine kinase in the PI3K family, regulates mitochondrial fusion and division by modulating fusion protein expression. Through the mTOR-MFN2-PKM2 pathway, mTOR promotes the interaction between MFN2 and PKM2, which is essential for glycolysis and oxidative phosphorylation in breast cancer cells.¹¹³ High OPA1 expression correlates with poor prognosis in breast cancer, whereas OPA1 inhibition reduces tumor growth, aggressiveness, and neovascularization, thereby inhibiting metastasis.¹¹⁴

Additionally, mitochondrial fusion exhibits anti-apoptotic activity, with fusion stimulation significantly delaying apoptosis.¹¹⁵ This process plays a critical role in breast cancer progression and presents promising therapeutic opportunities.^{116,117}

Mitochondrial dynamics, including fission and fusion, are closely associated with mitophagy, which facilitates the selective autophagic elimination of mitochondria. Mitophagy plays a vital role in cellular homeostasis by encapsulating and degrading damaged or dysfunctional mitochondria, preventing the accumulation of harmful protein aggregates and excessive ROS.¹¹⁸ This process maintains a healthy mitochondrial network, maintaining bioenergetic capacity and supporting overall cellular function. Mitophagy relies on mitochondrial fission, as evidenced by its inhibition through a dominant-negative Drp1 mutant.¹¹⁹ The selective removal of photodamaged mitochondria highlights fission's role

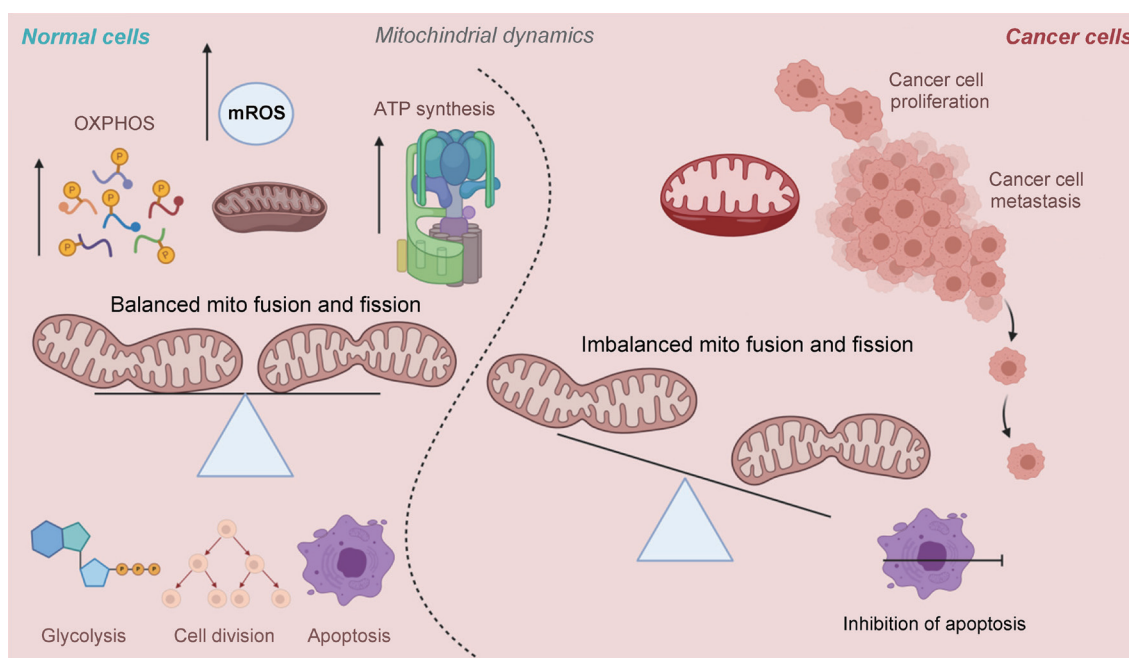


Fig. 1. Mitochondrial dynamics in normal and cancer cells. Mitochondrial dynamics, governed by the interplay of fission and fusion proteins, are essential for maintaining cellular function and homeostasis. Fission facilitates glycolysis, mitophagy, apoptosis, and cell division, while fusion supports ATP production and reactive oxygen species (ROS) generation through oxidative phosphorylation (OXPHOS). In normal cells, the equilibrium between mitochondrial fusion and fission ensures proper cellular health and function. However, in cancer cells, this balance is disrupted, with a shift toward increased fission. This imbalance fuels uncontrolled proliferation, metastasis, and the preservation of cancer stem cell phenotypes, underscoring the pivotal role of altered mitochondrial dynamics in cancer progression. ATP, adenosine triphosphate; mROS, mitochondrial reactive oxygen species. (The figure is adopted from Gundamaraju *et al.*,¹³⁵ 2021.)

as a quality control mechanism, isolating damaged segments for autophagic degradation while preserving a functional mitochondrial network.¹²⁰ Recent studies on breast cancer have highlighted the role of the PINK1 and Parkin genes in mitochondrial quality control through the targeted elimination of damaged mitochondria.^{121,122} PINK1 recruits the E3 ubiquitin ligase Parkin from the cytosol to damaged mitochondria, where Parkin ubiquitinates outer mitochondrial membrane proteins, marking the mitochondrion for autophagic degradation. In tumor cells, mitochondrial F1F0 ATPase can use glycolytic ATP to restore membrane potential, and mitochondrial fusion can compensate for missing components, rescuing impaired organelles.¹²³ However, mitochondrial fission can overwhelm these compensatory mechanisms, leading to complete depolarization and initiating PINK1-mediated mitophagy. This intricate process highlights the balance between mitochondrial dynamics, damage sensing, and quality control.¹²⁴

Additionally, accumulating evidence links intracellular ROS to tumor progression. Mitophagy plays a tumor-suppressive role by removing dysfunctional mitochondria and reducing ROS production in tumor cells.¹²⁵ For instance, ULK1 depletion in breast cancer cells impairs mitophagy, leading to excessive ROS accumulation. This aberrant ROS production activates the NLRP3 inflammasome, promoting breast cancer bone metastasis.¹²⁶ Recent studies have highlighted the role of BRCA1 as a tumor suppressor in regulating mitophagy. BRCA1 deficiency disrupts mitophagy by inhibiting mitochondrial fission, resulting in damaged mitochondria and elevated ROS levels, which activate the NLRP3 inflammasome, thereby promoting breast cancer metastasis.¹²⁷ Similarly, BNIP3 loss impairs mitophagy, leading to ROS accumulation and enhanced growth and metastasis of TNBC.¹²⁸ These findings sug-

gest that restoring mitophagy to reduce ROS could be a promising therapeutic strategy. Interestingly, certain drugs and compounds activate mitophagy to exert antitumor effects, further underscoring its role in cancer suppression.^{129,130} However, under metabolic stress or nutrient deprivation, mitophagy may promote tumor survival by enabling cancer cells to adapt. For instance, MRPL52 upregulation activates protective mitophagy via the PINK1/Parkin pathway, helping breast cancer cells survive hypoxia.¹³¹ Similarly, MUC1, located on the mitochondrial outer membrane, interacts with ATAD3A to promote PINK1-dependent mitophagy. Inhibiting either MUC1 or mitophagy alone reduces tumor proliferation, but combined inhibition demonstrates enhanced suppression of breast tumor growth both *in vitro* and *in vivo*.¹³² These findings reveal the dual role of mitophagy in breast cancer, acting as a tumor suppressor by reducing ROS and eliminating damaged mitochondria and as a survival mechanism under adverse conditions.¹³³ Combining mitophagy modulation with therapies targeting mitochondrial fission and fusion offers a promising avenue for breast cancer treatment.

Mitochondrial dynamics as a therapeutic target in breast cancer metastasis

Mitochondrial dynamics, including fusion, fission, and mitophagy, are integral to tumor signaling pathways and mitochondrial metabolism, playing a critical role in cellular adaptability.¹³⁴ In normal cells, a balance between mitochondrial fusion and fission maintains homeostasis. However, in cancer cells, this balance is disrupted, driving proliferation, metastasis, and cancer stem cell maintenance (Fig. 1).¹³⁵ In TNBC, studies have inves-

Table 1. Current therapies or regulators that actively modulate mitochondrial fission, fusion, and mitophagy in breast cancer

Targeted therapy/drug candidate	Functional target	Cancer target	References
Gene knockdown	Fission	Breast cancer	148
Hypoxia	Fission	MDA-MB-231	149
Cisplatin	Fission	TNBC	150
Mdivi-1 (mito division inhibitor 1)	Fission	Breast and lung	151
Paclitaxel	Fission	Breast cancer	152
Isotoosendanin	Fission	TNBC	153
P110 (peptide inhibitor)	Fission	Breast cancer	154
Dynsore	Fission	TNBC	155
BRCA1 (breast cancer associated gene 1)	Fusion	MDA-MB-231	127
RACGAP1/LncRNA (long non-coding RNAs)	Fission and fusion	MCF-7 and MDA-MB-231	86
MiR-195 (microRNA 195)	Fission and fusion	MCF-7 and MDA-MB-231	116
MiDs (mito dynamics)	Fission and fusion	MCF-7	156
PKM2 (pyruvate kinase M 2)	Fusion	MCF-7	157
Silibinin	Fusion and mitophagy	MCF-7 and MDA-MB-231	158
Polyphyllin I	Mitophagy	MCF-7 and MDA-MB-231	159
Warangalone	Mitophagy	MCF-7 and MDA-MB-231	122
Flubendazole	Mitophagy	MCF-7 and MDA-MB-231	160
Taloxifene	Mitophagy	MCF-7	161
Cepharanthine	Mitophagy	MDA-MB-231	162
Kaempferol	Mitophagy	MCF-10AT	130
Costunolide	Mitophagy	MCF-7	163
Copper complex CPT8	Mitophagy	MDA-MB-231	164
Ru-TPE-PPh complex	Mitophagy	MDA-MB-231	165
Baicalein	Mitophagy	MDA-MB-231	166
Acid ground nano-realgar processed product	Mitophagy	MDA-MB-435S	129

TNBC, triple-negative breast cancer.

tigated alterations in mitochondrial dynamics, revealing significant variability in their expression.^{105,136} However, the connection between mitochondrial dynamics and metabolic phenotypes remains inconsistent across different breast cancer models and studies.^{137,138} Mitophagy, the selective autophagy of mitochondria, is essential for maintaining intracellular stability by removing damaged or dysfunctional mitochondria, thereby preserving cellular homeostasis.¹³⁹ Targeted mitochondrial therapy shows promise, as mitochondrial fission is linked to poor breast cancer prognosis. Inhibiting fission has demonstrated the potential to reduce metastasis, presenting a novel therapeutic strategy.¹⁴⁰ The small molecule Mdivi-1 binds to Drp1, suppressing mitochondrial fission, lowering ATP production, and inducing apoptosis in breast cancer cells.¹⁴¹ Additionally, the peptide inhibitor P110 blocks the Drp1-Fis1 interaction, effectively halting fission. With fewer side effects than Mdivi-1, P110 holds greater potential for clinical application.¹⁴² Promoting mitochondrial fusion has been shown to enhance TNBC sensitivity to chemotherapy. In mice with MDA-MB-231 breast cancer cells, injections of P-Mito or Mdivi-1 increased sensitivity to doxorubicin to a similar extent.¹⁴³ The poor prognosis of TNBC is linked to

its high aggressiveness, partly driven by elevated ROS levels. Studies indicate that reducing ROS content in cancer cells can attenuate metastasis.¹⁴⁴ Mitochondrial peroxide-reducing proteins, particularly Prdx3 and Prdx5, are often upregulated in various cancers, contributing to drug resistance.^{145,146} Mitochondrial transplantation also represents a novel approach to breast cancer treatment, potentially mitigating the toxic side effects of conventional therapies.¹⁴⁷ However, the complexity of this method currently limits its clinical application. Table 1 provides an overview of the key regulators and emerging therapeutic strategies targeting mitochondrial fission, fusion, and mitophagy in breast cancer.^{86,116,122,127,129,130,148–166}

Clinical significance and prospects

Recent research underscores the pivotal role of mitochondrial dynamics and bioenergetics in a wide range of diseases, extending far beyond cancer progression.^{167–170} Cancer cells rely on altered mitochondrial function and oxidative metabolism to fuel proliferation and tumorigenesis.¹⁷¹ They demonstrate elevated oxidative

phosphorylation and disrupted mitochondrial dynamics, including increased fission, decreased fusion, and enhanced mitophagy, making these processes promising therapeutic targets. While interventions targeting oxidative phosphorylation, the TCA cycle, and mitochondrial dynamics have been investigated, their clinical efficacy is often undermined by drug resistance.¹⁷² Understanding mitochondrial dynamics and bioenergetics in breast cancer is key to advancing personalized treatments. Future research should focus on unraveling the roles of mitochondria in cellular metabolism, cancer progression, and therapy resistance. Insights into metabolic flexibility and the regulation of mitochondrial function are crucial for enhancing therapeutic efficacy. Additionally, exploring the physiological factors influencing mitochondrial fitness will be vital for optimizing targeted therapies and improving outcomes for breast cancer patients.

In metastatic breast cancer, an imbalance in mitochondrial dynamics plays a pivotal role.^{78,173} Experimental studies reveal that metastatic breast cancer cells exhibit heightened mitochondrial fission, reduced fusion, and increased fragmentation. These alterations underscore the potential of targeting mitochondrial processes in breast cancer treatment.^{46,174} Despite significant progress in understanding mitochondrial dynamics and mitophagy in tumor progression, key questions remain unresolved. Emerging evidence highlights the complex and context-dependent roles of these processes, which vary by tumor type, stage, and microenvironment. Further research is essential to elucidate how mitochondrial dynamics drive metastatic cancer progression and how these mechanisms can be targeted with greater precision. Advancing knowledge in this area holds the potential to develop more effective, targeted therapies, addressing current treatment challenges and improving outcomes for breast cancer patients.

Conclusions

This review highlights the pivotal role of mitochondrial dynamics and bioenergetics in driving breast cancer progression and metastasis. By elucidating the intricate interplay between mitochondrial functions—biogenesis, turnover, fission, fusion, mitophagy, oxidative stress regulation, metabolism, and ATP synthesis—it reveals the critical regulatory mechanisms that fuel cancer cell adaptation. Targeting these processes presents promising therapeutic opportunities, paving the way for mitochondria-focused strategies to enhance drug efficacy and improve treatment outcomes. Ultimately, this comprehensive analysis underscores the potential of mitochondrial-directed interventions as a transformative approach in breast cancer therapy.

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