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A review of the pathogenesis of mitochondria in breast cancer and progress of targeting mitochondria for breast cancer treatment

Aoling Huang[1†], Haochen Xue[1†], Ting Xie[1], Lingyan Xiang[1], Zhengzhuo Chen[1], Aolong Ma[1], Honglin Yan[1] and Jingping Yuan[1*]

Abstract

With breast cancer being the most common tumor among women in the world today, it is also the leading cause of cancer-related deaths. Standard treatments include chemotherapy, surgery, endocrine therapy, and targeted therapy. However, the heterogeneity, drug resistance, and poor prognosis of breast cancer highlight an urgent need for further exploration of its underlying mechanisms. Mitochondria, highly dynamic intracellular organelles, play a pivotal role in maintaining cellular energy metabolism. Altered mitochondrial function plays a critical role in various diseases, and recent studies have elucidated its pathophysiological mechanisms in breast carcinogenesis. This review explores the role of mitochondrial dysfunction in breast cancer pathogenesis and assesses potential mitochondria-targeted therapies.

Keywords Mitochondria, Mitochondrial dynamics, Breast cancer, Mitochondrial metabolism, Apoptosis

Introduction

Breast cancer is one of the most prevalent cancers in the world and is a significant cause of cancer deaths in women, with serious implications for women's quality of life [1, 2]. However, late-stage breast cancer with systemic metastasis markedly increases patient mortality [3]. Breast cancer is broadly classified into invasive and non-invasive types, and invasive breast cancer is further categorized into molecular subtypes: hormone receptor-positive (estrogen receptor [ER+] or progesterone receptor [PR+]), human epidermal receptor2-positive (HER2+) and triple-negative (ER-, PR-, and HER2-) [4, 5]. Numerous preclinical and clinical studies have highlighted the roles of genetic factors, reproductive factors and lifestyle habits, such as diet, in breast cancer development [6, 7]. As research progresses, factors related to the body's metabolic functions, such as adipose tissue, chronic inflammation, glycolysis and oxidative phosphorylation, are increasingly recognized as critical to breast cancer development [8, 9]. Despite recent breakthroughs in the diagnosis and treatment of breast cancer, including surgery and radiotherapy, a large proportion of patients with distant metastases remain incurable. The mortality rate for metastatic breast cancer is extremely high, exceeding 90% of the overall breast cancer mortality rate [10, 11]. Further research is needed on how cancer cells survive and the mechanisms behind metastasis.

Mitochondria play a pivotal role in the metabolic reprogramming of cancer cells, particularly in energy production, redox control, and cell death regulation [12, 13]. Understanding mitochondrial function in breast

†Aoling Huang and Haochen Xue contributed equally to this work.

*Correspondence:
Jingping Yuan
yuanjingping@whu.edu.cn
[1]Department of Pathology, Renmin Hospital of Wuhan University, 238 Jiefang-Road, Wuchang District, Wuhan 430060, P. R. China

cancer could provide new insights into the mechanisms of metastasis and potential therapeutic strategies. Mitochondrial DNA (MtDNA), the genetic material of mitochondria, is a small circular DNA (16,569 kb in humans) present in multiple copies within each mitochondrion [14]. In structure, the mitochondrion consists of a two-membrane system: an inner membrane and an outer membrane, with the mitochondrial cristae forming between them. These cristae house numerous enzymes involved in oxidative phosphorylation, which generate energy for adenosine triphosphate (ATP) production through electron transfer from respiratory chain complexes [15]. Additionally, mitochondria-controlled release of reactive oxygen species (ROS) can disrupt cellular homeostasis and contribute to the pathogenesis of various diseases [16]. Breast cancer, a heterogeneous disease shaped by environmental and intrinsic biological factors, is closely linked to disruptions in energy metabolism, particularly glycolysis and oxidative phosphorylation. While these metabolic alterations significantly contribute to the aggressiveness and progression of the disease, the precise mechanisms underlying mitochondrial metabolic functions in breast cancer remain unclear. Nevertheless, understanding these mechanisms is critical for developing effective strategies targeting mitochondria in breast cancer therapy.

This review summarizes the recent advances in mitochondrial dynamics and its metabolic processes in the diagnosis and treatment, highlights the role of mitochondria dysfunction in breast cancer pathogenesis, and explores their potential as therapeutic targets for both early-stage breast cancer and recurrent metastatic disease.

Basic mechanisms of mitochondrial dysfunction in cancer

Mitochondria are essential organelles that play a central role in regulating complex physiological processes in the body. Notably, the recognition of mitochondrial dysfunction in various diseases has sparked a surge of interest in mitochondria-targeted therapies in recent years [17]. Specifically, key therapeutic strategies include direct modulation of mitochondrial dynamics, resistance to oxidative stress levels and alteration in energy metabolic processes. Furthermore, mitochondria are deeply involved in numerous biological processes, such as mitochondrial quality control (MQC) systems (including biogenesis, dynamics, autophagy), mtDNA maintenance, synthesis of mitochondria-associated proteins, enzyme activity, metabolic signaling, ATP production and calcium regulation [18]. These mitochondria-specific processes are illustrated in Fig. 1, highlighting their multifaceted roles in cellular function and homeostasis.

The molecular mechanisms of mitochondrial dysfunction primarily stem from imbalances in the MQC system, metabolic dysregulation, excessive ROS production and disturbances in calcium homeostasis [18]. During tumorigenesis and progression, tumor cells exhibit increasingly rely on glycolysis [19], leading to mitochondrial metabolism reprogramming to meet the needs of rapid cancer cell growth. This reprogramming not only support tumor growth but also increase the risk of metastasis [20]. Furthermore, the metabolic processes of the mitochondria are highly complex, allowing cancer cells to adapt by co-utilizing both oxidative phosphorylation and glycolysis to fulfill their biological requirements [21]. Additionally, dysregulated mitochondrial oxidative stress elevates ROS levels, which in turn damage mtDNA and triggers a feedback loop that further amplifies ROS production [22]. These processes can provoke inflammatory responses, suppress the immune system, and enable cancer cells to evade of the immune clearance, ultimately facilitate the metastasis [23]. Moreover, mitochondrial dysfunction in immune cells impairs their function, rendering them inactive and further contributing to tumor immune evasion [24]. Collectively, these findings underscore the critical role of mitochondrial dysfunction in cancer development. Breast cancer is a heterogeneous disease influenced by both environmental factors and intrinsic biological alterations within the organism [25]. Among these, disruptions in energy metabolism play a pivotal role in driving the aggressiveness and progression of breast cancer. Notably, changes in glycolysis and oxidative phosphorylation are key indicators of these metabolic alterations. However, the precise relationship between breast cancer and the Warburg effect remains inadequately understood [26]. Moreover, chronic inflammation, oxidative stress, and metabolic imbalances have been identified as significant contributors to breast cancer pathogenesis. In this context, mitochondrial alterations are increasingly recognized as critical factors. As a result, targeting mitochondrial function has emerged as a promising therapeutic strategy in breast cancer treatment. Given the high incidence of breast cancer, its substantial risk of metastasis, and the poor prognosis associated with specific subtypes, this review aims to provide a comprehensive overview. Specifically, it will explore the pathological mechanisms underlying mitochondrial dysfunction in breast cancer and highlight recent advancements in mitochondria-targeted therapies, offering new insights into potential clinical applications.

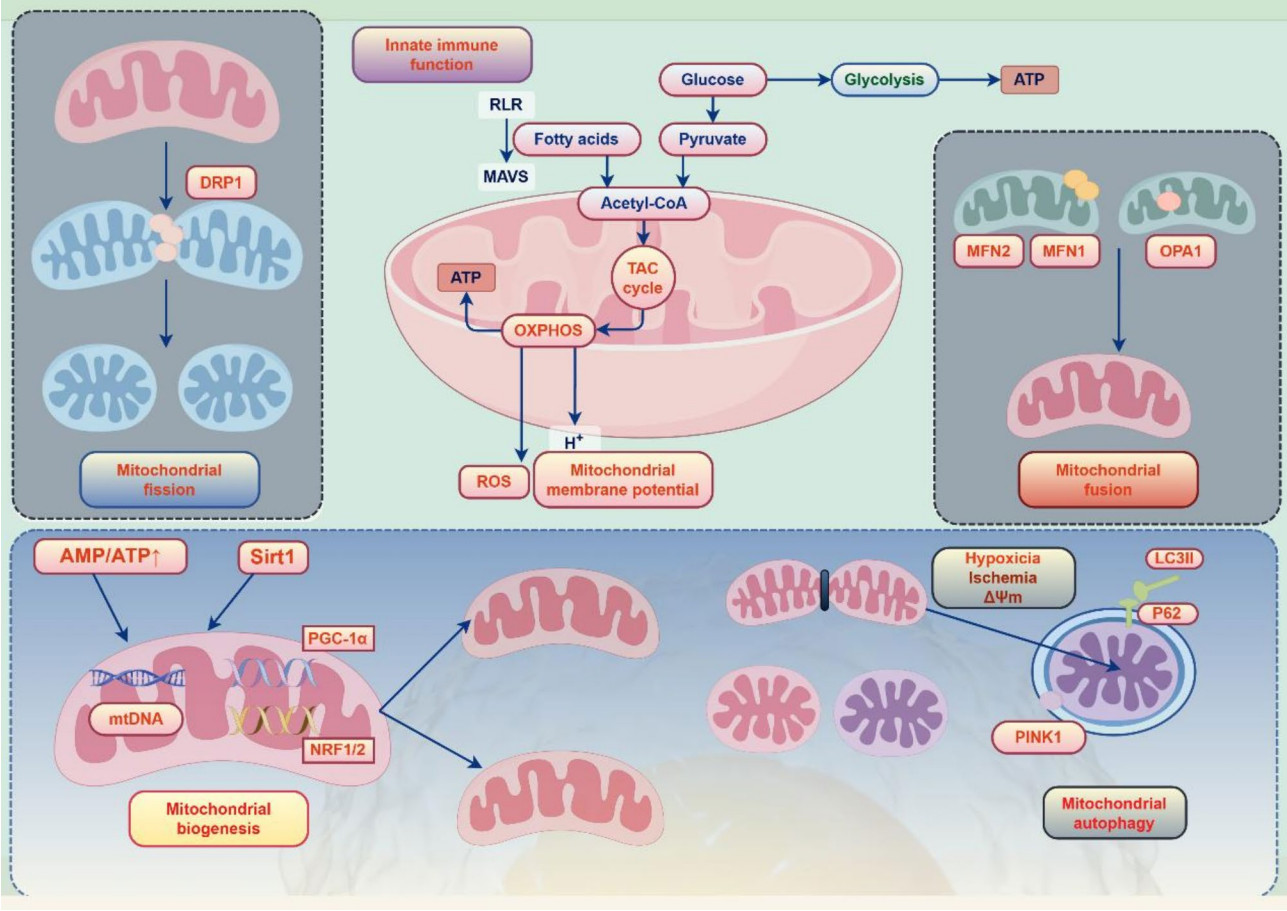

Fig. 1 Physiological functions of mitochondria

The role of mitochondria dysfunction in breast cancer

Alterations of mtDNA and mtDNA copy number in breast cancer

MtDNA plays a crucial role in encoding oxidative phosphorylation, which is essential for ATP production [27]. Damage to mtDNA or a reduction in its copy number can result in various diseases, including aging, neurodegenerative diseases and diabetes [28–30]. In recent years, there has been growing interest in studying mtDNA in breast cancer. Novel techniques for detecting mtDNA expression have shown promising applications in breast cancer diagnosis. For instance, a dual qPCR assay based on TaqMan probes can quantify circulating free mtDNA. By incorporating machine learning methods to construct models linked to clinical features, this approach demonstrates high diagnostic value for breast cancer [31]. While circulating free mtDNA has long been used as a biomarker for a various cancers [32, 33], advancements in technology are expected to enhance the accuracy and clinical feasibility of breast cancer diagnostics.

In addition to its diagnosis importance, mtDNA also plays a critical role in the treatment of breast cancer. For instance, a carbazole-based fluorescent ligand targeting mitochondria has been developed. This ligand induces mtDNA depletion, reduces ATP levels and disrupts ROS balance, ultimately triggering tumor cell apoptosis and autophagy, thereby exerting anti-breast cancer effects [34]. Additionally, a novel technique involving mitochondria-targeted RNAi nanoplatforms has been introduced. These nanoplatforms transport small interfering RNA (siRNAs) into mitochondria, downregulating proteins encoded by mtDNA under the protection of polyethylene glycol and the action of membrane-penetrating peptides. This approach induces mitochondrial damage in tumor cells, with a potential mechanism being the repolarization of tumor-associated macrophages (TAMs) into tumor-suppressive M1-like macrophages [35]. Given the unique characteristics of triple-negative breast cancer (TNBC), further exploration of meaningful therapeutic targets is warranted. Enhancing mitochondrial function may become a crucial focus in future research. For example, targeting Elongin B effectively regulates mtDNA expression, improving mitochondrial function and leading to better outcomes for TNBC patients following radiation therapy [36]. The advancement of mitochondria-targeted

technologies and drug delivery platforms offers promising options for breast cancer treatment.

The mtDNA exists in copy number, and the assessment of mtDNA copy number helps to understand the diseases brought about by variations in mtDNA [37]. A cohort study has found that mtDNA copy number mediates the relationship between perfluoroalkyl substances and the incidence of breast cancer, which offers some possibilities for explaining the pathogenesis of breast cancer [38]. Similarly to this, an elevated mtDNA copy number in leukocytes correlated with poor prognosis in breast cancer patients, in particular breast cancer patients with higher mtDNA copy number in leukocytes have significantly lower disease-free survival than patients with lower mtDNA copy number [39]. However, an increased frequency of mitochondrial defects, including decreased mtDNA content, reduced mtDNA copy number and sequence imbalance, has been identified in TNBC, which contributed to impaired cellular mitochondrial function and a metabolic transition toward glycolysis, leading to tumorigenesis [40]. The reason for this difference compared to previous conclusions may lie in the distinction between breast cancer subtypes, including TNBC, Luminal and HER2 + subtypes that may have different mitochondrial defects affecting the risk of breast cancer metastasis. These studies revealed the possibility of mtDNA copy number as a disease marker in breast cancer, providing a valuable reference for the prognosis of breast cancer patients.

Studies have also emerged in the treatment of targeting mtDNA copy number. Knockdown of pyrroline-5-carboxylate reductase 3 (PYCR3) in TNBC was investigated to regulate mtDNA copy number, thereby reducing cell proliferation and reversing doxorubicin resistance in TNBC [41]. This study provides a new perspective on drug resistance in TNBC, and the use of PYCR3 as a new starting point to modulate mtDNA copy number may become a new therapeutic tool. In studies related to breast cancer metastasis, inhibition of lipogenesis and a metabolic shift in favor of ATP production may be an crucial factor in epithelial-mesenchymal transition in breast cancer and a significant elevation in the level of mtDNA copy number would be favorable for energy production [42]. These studies provide new insights into the role of mtDNA copy number in the treatment of breast cancer and enhance the understanding of mtDNA copy number in mitochondrial energy production in breast cancer.

Alterations in the mitochondrial quality control system in breast cancer

The MQC system has been shown to play a critical role in tumor progression and metastasis [43, 44]. Mitochondrial morphology is dynamically regulated by the processes of fission and fusion [45]. A network of healthy mitochondria maintains a balanced state through these mechanisms: fission and autophagy help remove damaged mitochondria, while fusion allows the mixing of mtDNA to preserve functional genes and ensure proper cellular function [46–48].

Studies on mitochondrial dynamics reveal subtype-specific variations in breast cancer. For instance, in luminal breast cancer, silencing of NADPH oxidase 4 (NOX4) elevates ROS levels, promoting adenocarcinoma cell migration and invasion [49]. Reduced dynamin-related protein 1 (DRP1)-mediated mitochondrial fission in luminal breast cancer cells may result in altered mitochondrial morphology. In contrast, the basal-like breast cancer subtype, although less common, is associated with a much poorer prognosis. Notably, proteomic analysis has revealed differences in the expression of mitochondrial complexes I and V between basal-like and luminal A subtypes, aiding in distinguishing these tumors and highlighting the diagnostic value of mitochondrial profiling [50]. Furthermore, in TNBC, high basal autophagy and enhanced mitochondrial fission promote cancer cell migration [51]. For example, a slow-release H2S donor, 5-(4-hydroxyphenyl)-3 H-1,2-dithiolane-3-thione, has been shown to suppress autophagosome formation, improve autophagic flux, and elongate mitochondria by reducing Drp1expression while increasing Mitofusin 2 (MFN2) expression. As a result, this treatment effectively inhibits TNBC cell migration and invasion [52]. These findings collectively underscore the importance of mitochondrial dynamics across breast cancer subtypes. Specifically, increased autophagy and mitochondrial fission can favor tumor growth, whereas breast cancers with low metastatic potential exhibit longer mitochondrial lengths. Moreover, the specific removal of mitochondrial fission mediators appears to hinder metastasis [53]. Additionally, knocking down fission-associated genes can alter cancer cell metabolites and impair oxidative phosphorylation (OXPHOS). Interestingly, treatment with the mitochondrial division inhibitor (mdivi-1) reduces proliferation and clonogenic capacity by inducing cancer cells to detach and float [54], drawing attention to overlooked floating cancer cells separated from the extracellular matrix.

In addition to this, drug resistance remains a major obstacle in the treatment of breast cancer, exemplified by resistance to tamoxifen (TAM) in estrogen-sensitive breast cancer patients. Studies have found that high expression of MFN1 is associated with poor prognosis in breast cancer patients, with particularly significant upregulation observed in TAM-resistant cells [55]. However, pharmacological inhibition of Mitofusin 1 (MFN1) expression has been shown to prevent mitochondrial fusion, amplify caspase-3/9 activation, restore

drug-resistant cells' sensitivity to apoptosis, and enhance the therapeutic efficacy of TAM. This finding highlights the impact of altered mitochondrial dynamics on breast cancer drug resistance from the perspective of mitochondrial fusion and suggests a potential strategy for overcoming TAM resistance in breast cancer treatment. Beyond changes in mitochondrial structure caused by mitochondrial dynamics, interactions between organelles may also influence mitochondrial function. GOLPH3, a Golgi protein that interacts with phosphatidylinositol 4-phosphate, is significantly elevated in breast cancer. Knockdown of GOLPH3 disrupts the mitochondrial network, reduces bioenergetic function, affects mitochondrial fission, and alters energy metabolism in breast cancer cells [56]. This discovery sheds light on the crucial interplay between the Golgi apparatus and mitochondria in breast cancer development, providing new insights into the mechanisms underlying tumor progression.

Mitochondrial autophagy is another crucial component of the MQC system. It plays an essential role in maintaining normal cellular function by mediating the clearance of damaged or senescent mitochondria [57]. However, abnormal activation of mitochondrial autophagy can lead to genomic destabilization and increase susceptibility to various cancers [58]. Among the known mechanisms, Parkin/PTEN-induced putative kinase 1 (PINK1)-mediated mitochondrial autophagy is relatively common. For instance, a softer extracellular matrix has been shown to induce DRP1 translocation-triggered mitochondrial fission and PINK1-Parkin-mediated autophagy through enhanced calcium transport between the endoplasmic reticulum and mitochondria [59]. Interestingly, mitochondrial autophagy can have contrasting effects on tumor survival. On the one hand, it may attenuate tumor tissue necrosis and promote tumor survival. For example, mucin 1 (MUC1) interacts with ATAD3A, an enzyme of the ATPase family, to inhibit the cleavage of PTEN-induced PINK1, thereby inducing mitochondrial autophagy and enhancing cancer cell activity [60]. This mechanism highlights a potential therapeutic target for MUC1-positive breast cancer. On the other hand, excessive activation of mitochondrial autophagy can promote apoptosis and exert anti-tumor effects. For instance, drug-induced overactivation of PINK1-Parkin-mediated autophagy in TNBC cells has been shown to trigger apoptosis [61]. These findings demonstrate that overactivated autophagy can impair tumor cell survival. In contrast, disrupted autophagic flux may also have therapeutic implications. While normal autophagic flux generally promotes cancer cell proliferation, blocking autophagy through specific drugs has been associated with increased ferroptosis, ultimately inhibiting tumor growth [62]. Similarly, inhibiting mitochondrial autophagy has been shown to restore drug sensitivity in resistant cancer cells, providing a promising approach for overcoming drug resistance [63]. Moreover, mitochondrial autophagy holds potential for diagnostic applications. For example, a fluorescent biosensor designed to detect mitochondrial autophagy has been used to evaluate the therapeutic effects of drugs and assess the invasive capacity of cancer cells, offering valuable insights into breast cancer lung metastasis [64].

Mitochondria-mediated apoptosis or proliferation in breast cancer

Iron death, an oxidatively regulated form of cell death, is driven by elevated levels of iron-dependent lipid ROS, with mitochondria serving as a key site of ROS production [65]. Several studies have explored the potential of targeting mitochondria to induce iron death as a therapeutic strategy for breast cancer. For instance, salinomycin, an iron death-targeting drug, has been shown to eliminate breast cancer stem cells by triggering this pathway. Its primary target is the mitochondria, where its mechanism of action leads to the inhibition of mammalian target of rapamycin (mTOR), a key effector of salinomycin-induced iron death. This finding provides compelling evidence supporting the feasibility of targeting mitochondria-induced iron death in breast cancer treatment [66]. This treatment significantly alters iron death markers, including increased intracellular iron, lipid ROS, and malondialdehyde levels, alongside decreased glutathione levels and modifications in mitochondrial morphology [67]. Notably, the pronounced mitochondrial atrophy and upregulation of heme oxygenase-1 observed suggest that this drug not only alters mitochondrial function but also effectively induces iron death. These findings underscore the potential of mitochondria- and iron death-mediated therapies, offering new avenues for breast cancer treatment.

Cellular senescence plays an irreplaceable role in breast cancer proliferation, with sirtuin-1 (SIRT1) levels being closely related to cellular senescence in vivo. Notably, activation of SIRT1 can influence processes such as the cell cycle and cell death, effectively counteracting cellular senescence [68]. Moreover, neratinib, a classic small-molecule pan-human tyrosine kinase inhibitor approved for the treatment of HER2-positive breast cancer, has been shown to induce mitochondrial damage by increasing mitochondrial ROS levels, decreasing ATP production, and reducing telomerase activity [69]. Importantly, neratinib effectively lowers intracellular SIRT1 expression levels, significantly inducing senescence in breast cancer cells. Voltage-dependent anion channel protein 1 (VDAC1), a critical ion channel in mitochondria, also plays a pivotal role in normal mitochondrial function [70]. Interestingly, bioinformatics analyses have revealed that VDAC1 expression is higher in breast cancer

patients with poorer prognoses, suggesting its role in promoting breast cancer proliferation and migration. Therapeutic studies involving microRNAs (miRNAs), which are increasingly recognized as key regulators in breast cancer, have shown promising results. For example, miR-874-3p can regulate VDAC1 expression, effectively inhibiting the migration and proliferation of breast cancer cells [71]. Given the abnormal expression of miRNAs in breast cancer, further research into both oncogenic and oncostatic miRNAs is essential to explore their potential as small-molecule therapeutic agents. In addition to ion channels like VDAC1, metal ion channels are emerging as key therapeutic targets in breast cancer. For instance, the ion channel modulator isotretinoin induces breast cancer cell cycle arrest and apoptosis by affecting calcium channels and mitochondrial oxidative phosphorylation [72]. Since intracellular calcium homeostasis is crucial for breast cancer cell apoptosis and proliferation [73], altering calcium homeostasis through calcium channel modulation represents another potential strategy for inducing apoptosis in breast cancer cells.

The involvement of mitochondria in energy metabolism in breast cancer

Mitochondrial metabolic levels are often regarded as key targets for breast cancer treatment, given their central role in tumor progression. The Warburg effect, a hallmark of metabolic abnormalities in cancer, highlights the shift from oxidative phosphorylation to aerobic glycolysis, while mitochondrial respiration continues to contribute significantly to cancer progression [74, 75]. Therefore, targeting multiple processes within the mitochondrial metabolic pathway is increasingly recognized as integral to both the diagnosis and treatment of cancer [76, 77]. Dynein Light Chain Tctex-Type 1 (DYNLT1), a critical component in intracellular cargo transport along microtubules, has been found to be significantly upregulated in ER + and TNBC subtypes. Recent studies indicate that DYNLT1 promotes mitochondrial metabolism by inhibiting Parkin-mediated ubiquitination and degradation of VDAC1. Consequently, targeting DYNLT1 to suppress mitochondrial metabolism could enhance VDAC1 ubiquitination and degradation, thereby improving the efficacy of hypermetabolic inhibitors in cancer therapy [78]. In addition, the inhibition of mitochondrial inner membrane proteins (IMMT) has emerged as an important strategy for restraining breast cancer proliferation [79]. Studies demonstrate that IMMT inhibition reduces cell proliferation, disrupts mitochondrial cristae structure, and alters cellular metabolism. Notably, this approach suppresses glycolysis by modulating mitochondrial dynamics, further highlighting the potential of mitochondrial metabolic interventions in breast cancer treatment.

Mitochondrial biogenesis plays a critical role in mitochondrial metabolic functioning and is increasingly implicated in breast cancer development [80]. Beyond cancer cells themselves, cancer-associated fibroblasts (CAFs) in the immune microenvironment significantly influence mitochondrial biogenesis and tumor progression. For instance, CAFs have been shown to induce TNBC mitochondrial biogenesis and metastasis by promoting PGC-1α expression and its interaction with estrogen-related receptor α [81]. This suggests that PGC-1α could serve as a novel therapeutic target for TNBC. During cellular metabolism, oxidative phosphorylation enzymes also emerge as pivotal carcinogenic targets. For example, wild-type isocitrate dehydrogenase (IDH2) is overexpressed in TNBC, where it promotes tumor proliferation in vitro and in vivo. Inhibiting IDH2 elevates α-ketoglutarate (α-KG), disrupts the tricarboxylic acid cycle, reduces ATP production, and impairs glycolysis by promoting HIF-1α degradation, ultimately resulting in significant tumor suppression [82]. Similarly, mitochondrial creatine kinase (CKMT1) is upregulated in primary breast tumors but downregulated in metastatic tumors, with its depletion leading to elevated mitochondrial ROS and increased metastatic potential [83]. Early detection of creatine metabolites may thus help assess metastatic risk.

Potassium channels within the inner mitochondrial membrane also contribute to breast cancer development. Voltage- and calcium-activated large-conductance potassium channels regulate cellular energy metabolism and mediate the Warburg effect, promoting breast cancer progression under both aerobic and anaerobic conditions [84]. These findings underscore the importance of mitochondrial membrane proteins as actionable targets for cancer therapy. Changes in proteins in the inner and outer mitochondrial membranes will have a major impact on cellular metabolism, many of which are regulated by tumor cells, and the emergence of more useful targets will also facilitate the development of new medicines.

Additionally, bioinformatics studies have identified several metabolism-related genes critical to breast cancer proliferation. Several studies on metabolic enzymes have been conducted in breast cancer. For instance, analysis of public datasets has revealed that 7-dehydrocholesterol reductase (DHCR7) is strongly associated with immune infiltration and poor prognosis, while its knockdown significantly inhibits tumor growth [85]. Similarly, hypoxia-induced mitochondrial translocation of prolyl hydroxylase EglN1 (PHD2) was found to drive breast tumor growth. Proteomic studies show that EglN1 interacts with AMP-activated protein kinase α (AMPKα), inducing mitochondrial translocation and enhancing tumor adaptation to hypoxic environments [86]. This alteration is an adaptation of tumor cells to hypoxia, by

altering their own mitochondrial metabolism to adapt to the altered environment and thus ensure their growth. This also suggests new research horizons for researchers, focusing on altered mitochondrial metabolic processes in drug-resistant breast cancer may lead to the discovery of more novel targets. In TNBC, hypoxia further alters glycogen metabolism. Glycogen synthase 1 (GYS1) is significantly upregulated in TNBC, correlating with poor survival rates. Inhibiting GYS1 suppresses TNBC proliferation by disrupting glycogen synthesis and mitochondrial homeostasis [87]. Down-regulation of GYS1, however, brings about inhibition of breast cancer cell proliferation, mainly due to the process of glycogen synthesis by affecting mitochondrial homeostasis. This underscores the potential of targeting glycogen metabolism, alongside glycolysis and oxidative phosphorylation, in breast cancer therapies.

Surprisingly, research has also highlighted the metabolic profiles of cancer-associated adipose tissue. Malignant tumor-associated adipose tissues exhibit reduced levels of pyruvate dehydrogenase and citrate synthase compared to normal adipose tissues, correlating strongly with tumorigenesis [88]. Additionally, obesity exacerbates these metabolic shifts, synchronizing changes in cancerous adipose tissues with tumor progression. This emphasizes the need to monitor tumorigenesis in obese women and to consider adipose tissue metabolism in breast cancer research.

The role of mitochondria in breast cancer metastasis

Metastasis of breast cancer remains one of the most severe clinical challenges, for which effective solutions are still lacking. Metastatic recurrence occurs in a significant number of patients initially diagnosed as disease-free, posing a persistent threat to long-term survival [89]. Mitochondria, as the primary source of energy for cellular activities, play an essential role in cancer metastasis, which is intricately linked to mitochondrial function. Cancer cells exploit altered mitochondrial dynamics to meet their energy demands and adapt to diverse environments, enabling survival and proliferation under adverse conditions [90].

Notably, approximately 25–50% of patients with advanced breast cancer eventually develop brain metastases—a particularly lethal form of metastasis affecting the central nervous system. Studies have revealed a marked increase in phosphorylated DRP1 expression in brain metastases compared to primary tumors. This elevated mitochondrial fragmentation leads to impaired fatty acid oxidation and mitochondrial dysfunction [91]. The use of Mdivi-1, a DRP1 inhibitor, has shown limited efficacy, causing only a slight delay in metastatic recurrence. Mitochondrial fission is a crucial process in which mitochondria fragment into smaller units; damaged mitochondria are subsequently eliminated by mitophagy, while functional fragments may fuse to maintain mitochondrial integrity and cellular function. The identification of DRP1 as a potential therapeutic target offers promising avenues for the treatment of metastatic breast cancer, underscoring the importance of continued research into mitochondrial dynamics.

In addition to brain metastases, the lungs are another common site for TNBC metastasis [92]. Research has identified the response gene to complement 32 (RGCC) as significantly upregulated in lung metastatic tumor cells. RGCC enhances Polo-like kinase 1 activity and phosphorylates AMPKα2, thereby facilitating the lung metastasis of TNBC cells. Mechanistic studies have further shown that mitochondrial oxidative phosphorylation is upregulated in this context, providing sufficient energy to support tumor cell metastasis [93]. Consequently, limiting mitochondrial oxidative phosphorylation by targeting RGCC and its downstream signaling pathways has emerged as a key strategy to combat breast cancer lung metastasis. Metabolic reprogramming also plays a pivotal role in cancer progression [94]. As mitochondria are central to energy production, their critical importance cannot be overstated. Targeting mitochondrial oxidative phosphorylation or glycolysis to disrupt tumor cell development and invasiveness has become a major focus in cancer treatment research. The development of drugs aimed at these pathways is actively underway, offering hope for more effective strategies to control tumor metastasis.

Targeting mitochondria for therapeutic treatment in breast cancer

We have summarized the virous role mitochondria play in the pathogenesis of breast cancer, including alterations in mtDNA and mtDNA copy number, disruptions in the MQC system, and mitochondria-mediated changes in cell proliferation, apoptosis, and energy metabolism. The specific mechanism is shown in Fig. 2. Dysregulation of cellular metabolism has long been recognized as one of the hallmarks features of cancer development [95]. Mitochondria produce substantial amounts of ATP to maintain normal energy in the body through the OXPHOS process. However, the Warburg effect shifts cancer cells toward aerobic glycolysis, favoring the production of energy through this less efficient process [96, 97]. Given the pivotal role of mitochondrial metabolic processes in tumor cell growth and their critical involvement in the pathogenesis of breast cancer, the development of strategies targeting mitochondrial function has emerged as a promising avenue for breast cancer treatment. Current drug research focuses on modulating mitochondrial metabolic functions, as well as on mitochondria-mediated apoptosis and tumor cell proliferation. Additionally,

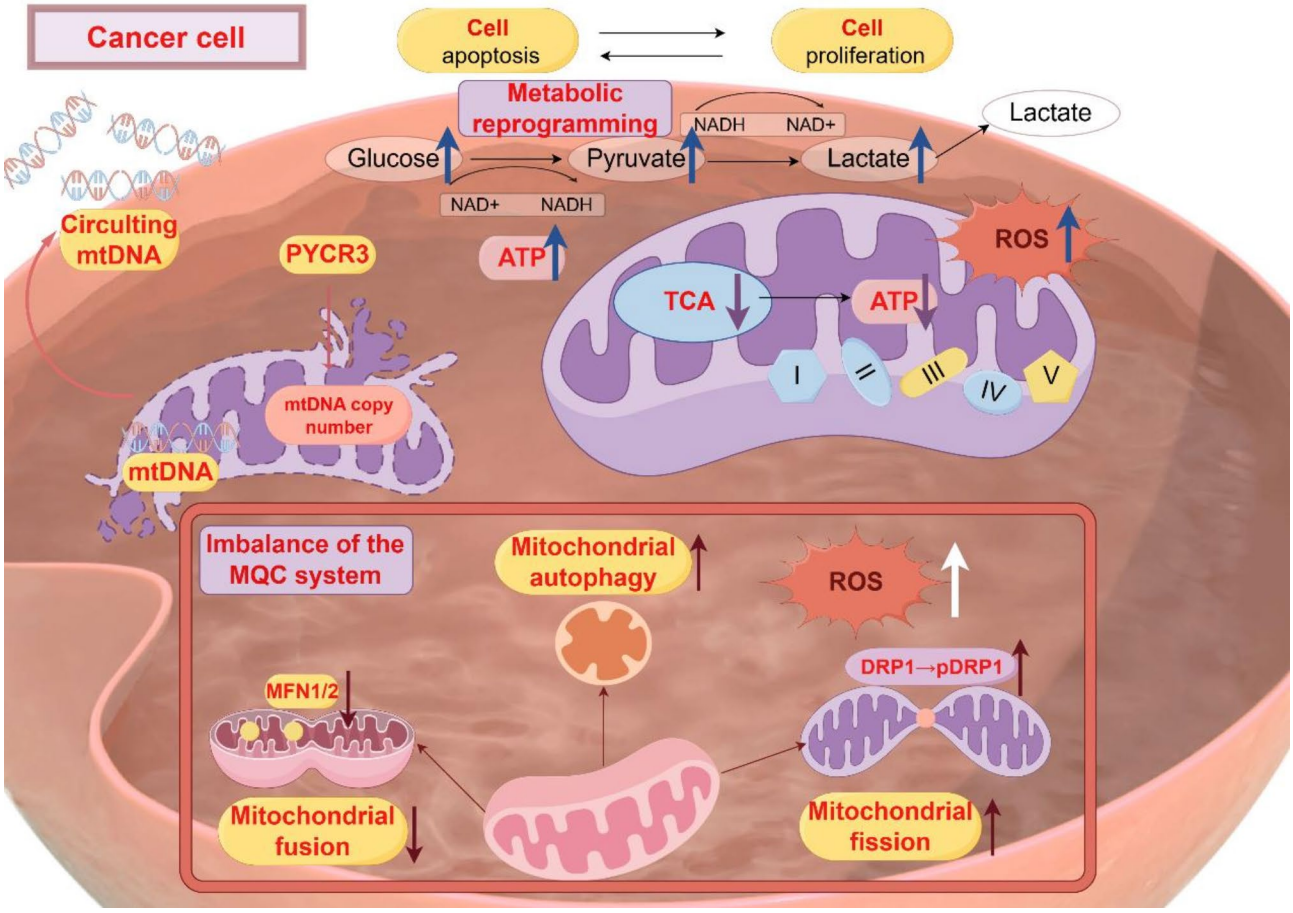

Fig. 2 Dysfunction of mitochondria in tumors

innovative nano-delivery systems are being designed to address drug resistance and mitigate the toxicity associated with conventional chemotherapeutic agents. This review aims to synthesize the primary functions and therapeutic mechanisms of these drugs, providing robust evidence to support current approaches targeting mitochondrial function in breast cancer treatment.

Targeting mitochondria mediates apoptosis or proliferation of tumor cells

By inducing apoptosis or limiting the proliferation of cancer cells, these are the principles of action of the common drugs currently used against cancer. Disarib, a specific BCL2 inhibitor, induces an increase in intrinsic ROS levels in TNBC, leading to apoptosis. The underlying mechanism of this effect may involve mitochondrial dysfunction and alterations in energy metabolism, which, in turn, affect epithelial-mesenchymal transition and angiogenesis [98]. Similarly, reduced graphene oxide and proteasome inhibitors (MG-132) are small molecule inhibitors that have shown promising anticancer effects in various breast cancer types, either alone or in combination [99]. The action of these inhibitors may result from the induction of oxidative stress in breast cancer cells, triggering apoptosis and necrosis, accompanied by changes in mitochondrial structure, offering a new avenue for breast cancer treatment.

Natural compounds also play a critical role in inducing apoptosis in breast cancer. Caged xanthones, a class of natural metabolites, exhibit strong antiproliferative properties against a broad spectrum of breast cancer cells. The mechanisms behind their activity likely include induction of G2/M cell cycle arrest and initiation of mitochondria-mediated apoptosis [100]. Another functional group-rich compound, Bruceine A (BA), significantly disrupts mitochondrial function, increases ROS production, decreases ATP levels, and induces mitochondrial apoptosis, leading to substantial inhibition of the proliferation of several breast cancer cell lines [101]. Molecular docking studies suggest that BA exerts its effects through the MEK/ERK pathways in cancer cells [102]. This drug has demonstrated superior efficacy compared to doxorubicin in vivo, suggesting that BA may offer a potential solution to overcoming drug resistance in TNBC. These studies provide strong evidence for the therapeutic value of small molecule inhibitors or natural compounds in inducing

Table 1 Nanodrugs targeting mitochondria for breast cancer treatment

Drugs	Formation	Targets	Methods
engineered mitochondrial targeted delivery system	Co-delivery of a natural K-channel agonist (Dinitrogen oxide, DZX) and an artificial K-channel molecule (5F8) via an amphiphilic mitochondria-targeted polymer (TMP)	potassium ion (K) channels	Selective delivery of drugs to cancer cell mitochondria specifically activates natural potassium channels and assembles artificial K-selective ion channels, thereby causing K influx to disrupt intracellular ion homeostasis
TNBC-specific targeted nano delivery agents	cRGD-labelled magnetic liposomes (T-LMD) with oleic acid-coated iron oxide nanoparticles (MN-OA) and doxorubicin (Dox)	iron/lipid metabolism pathway	Iron death nano-inducer (T-LMD) leads to membrane damage through enhanced ROS production, LDH and HMGB1 release while inducing mitochondrial alterations and enhanced DNA double-strand breaks
ATO/SRF@BSA	Developed by loading sorafenib and atovaquone into bovine serum albumin	inhibiting the glutathione peroxidase 4 (GPX4)-GSH pathway and downregulating the DHODH-coenzyme Q ($CoQH_2$) defense mechanism	Promotes accumulation of lipid peroxides in mitochondria and inhibits adenosine triphosphate (ATP) and pyrimidine nucleotide synthesis to inhibit cancer cell self-repair and enhance cell death.
LND-PLGA/TPS/DSSR NPs	Clonidamine (LND) was encapsulated in PLGA nanoparticles (NPs) encapsulated with mitochondria-targeted short chains (TPP-TPGS, TPS) and tumour-targeted long chains (DSPE-S-S-PEG2000-R6RGD, DSSR)	amaging mitochondria and releasing apoptosis-related proteins	Improving efficacy and bioavailability and reducing hepatotoxicity of LND
Ru-TPE-PPh_3	Synthesis via copper-catalysed cycloaddition of ruthenium nitride with alkynyl groups (CuAAC)	Excessive generation of reactive oxygen species (ROS)	Loss of mitochondrial membrane potential (MMP) and reduced adenosine triphosphate (ATP) production and onset of mitochondrial autophagy with autophagic flux blockage
COMET	Mitochondrial network disruption (MiND) nanoparticles (NPs) loaded with anti-MFN2 peptide, clindamycin and Bam7	Manipulation of intracellular communication and organelle fusion	Lowering the apoptotic threshold of MDR cells with MiND NPs, then inducing endoplasmic reticulum-mediated unfolded protein response (UPR) by stressing MDR cells with clindamycin, and finally inducing mitochondrial apoptosis with Bam7, a specific bcl-2 Bax activator.
9S1R nullomer peptide	9S1R peptide using alginate as a carrier	Mitochondrial TCA cycle/oxidative phosphorylation	Induction of mitochondrial structural and functional changes leading to deceleration of tumor metabolism
RP7	An antagonist peptide of the receptor for advanced glycosylation end products (RAGE)	RAGE	Inhibited the phosphorylation of ERK1/2, IKKα/β, IKBα and p65, blocked the NF-κB pathway, decreased the protein expression of Bcl-2 and HMGB1, and promoted the release of cytochrome C from mitochondria into the cytoplasm. Activated apoptosis in TNBC cells and inhibited epithelial-mesenchymal transition (EMT).

apoptosis or inhibiting breast cancer cell proliferation, and encourage researchers to focus on the development of novel compounds, which may help address the challenges of drug-resistant breast cancer treatment.

Construction of nanomedicine or delivery platforms targeting mitochondria

Delivery systems such as nanomaterials are increasingly demonstrating promising potential in the treatment of diseases. Nanoparticle-based drug delivery facilitates precise drug targeting while reducing adverse reactions. Several nano-delivery systems have been developed for the treatment of breast cancer, as summarized in Table 1.

An engineered mitochondria-targeted delivery system uses amphiphilic mitochondria-targeting molecules as carriers to co-deliver natural K-channel agonists (DZX) and artificial K-channel molecules (5F8), enhancing the influx of K ions and thereby disrupting mitochondrial function. This disruption involves a reduction in mitochondrial membrane potential, diminished ATP synthesis, and increased mitochondrial membrane permeability [103]. This delivery system significantly lowers the chances of tumor recurrence and reduces the probability of lung metastasis after surgical resection of breast tumors. In addition to delivering inhibitors targeting these cellular channels, creating platforms for the targeted delivery of chemotherapeutic drugs to minimize toxic side effects is also an effective strategy. Another iron death-inducing nanomedicine (ATO/SRF@BSA) has been developed by loading sorafenib (SRF) and atovaquone (ATO) into bovine serum albumin (BSA). This system triggers a burst of lipid peroxidation by inhibiting the glutathione peroxidase 4 (GPX4)-GSH pathway and down-regulating the DHODH-coenzyme Q pathway

[104]. This nano-delivery system not only kills tumor cells, but also avoids the toxic side effects of the drugs. As previously mentioned, although many clinical chemotherapeutic agents are available for cancer treatment, drug toxicity and lack of specificity still limit their use. These limitations can be overcome by utilizing targeted delivery systems. Lonidamine (LND) works by targeting mitochondria, but its limited solubility, lack of specificity, and potential hepatotoxicity have greatly restricted its clinical application. A glutathione-programmed mitochondria-targeted delivery platform for LND has been established, which effectively treats TNBC [105]. The nanomedicine effectively induced mitochondrial damage and apoptosis in tumor cells.

In addition to toxicities, drug resistance in TNBC remains a significant challenge that needs to be addressed. To combat drug resistance in TNBC, a researcher has designed a new metal-aromatic complex, Ru-TPE-PPh3, which effectively induces overproduction of ROS, leading to the loss of mitochondrial membrane potential (MMP) and disruption of cristae structure, ultimately triggering mitophagy [106]. Considering the clinical difficulty in treating TNBC, especially with its high recurrence rates, this novel nanomedicine targeting mitochondria may help mitigate this problem, potentially improving patient recovery post-surgery. A new approach to treating multidrug-resistant cancers involves manipulating intracellular communication and organelle fusion. Combinatorial Organelle Mitochondrial Endoplasmic Reticulum Therapy (COMET) is an innovative nanomedicine for treating multidrug-resistant TNBC. This synergistic triple-drug combination enhances the capacity of Bam7, a specific Bcl-2/Bax activator, to induce apoptosis selectively [107]. This complex of nanomedicines works in a multifaceted manner, not only inhibiting mitochondrial complexes in cancer cells but also avoiding toxic side effects. Another iron death-inducing nano-inducer specifically targets TNBC, boosting ROS production and inducing structural damage to mitochondria, which effectively kills cancer cells [108]. The emergence of more novel nanomedicines targeting TNBC will play a crucial role in addressing the high risk of metastasis and drug resistance in TNBC. However, further experimentation and safety evaluations are essential before these drugs can be used in clinical settings. Diagnosis of TNBC is equally important. A therapeutic diagnostic iron death inducer, IR780-SPhF, enables simultaneous imaging and treatment of TNBC by targeting the mitochondria. It also allows real-time monitoring of GSH levels in vivo and demonstrates a significantly stronger anticancer effect in vivo compared to cyclophosphamide [109]. Improving drug delivery efficiency is also a key goal in the development of new nanomedicines. A technology that accurately guides the release of doxorubicin through ultrasound imaging has been well-established, enabling precise release with higher drug-carrying efficiency in a smaller volume [110].

Moreover, small short-molecule peptides are emerging as potential drug candidates for breast cancer. Nullomer, a short peptide loaded onto alginate carriers, has demonstrated a unique anticancer effect on TNBC by inducing changes in the tumor immune microenvironment and targeting tumor metabolism. It down-regulates the mitochondrial tricarboxylic acid cycle pathway and ribosome biogenesis [111]. The receptor of advanced glycation end products (RAGE) is overexpressed in cancer, especially in TNBC [112]. A specific RAGE-binding peptide blocks activation of the nuclear factor kappa-B (NF-kB) signaling pathway, prevents the entry of p65 into the nucleus, and facilitates the release of cytochrome C from the mitochondria into the cytoplasm. This process activates apoptosis and inhibits epithelial-mesenchymal transition in TNBC cells [113]. Small-molecule peptide drugs are easier to develop, have lower toxicity, and may offer a more accessible path to clinical application. As more relevant studies emerge, many previously overlooked nanomedicines or small-molecule peptides are demonstrating promising therapeutic potential for the treatment of breast cancer.

Targeting mitochondrial in cellular metabolic

The exploration of drug resistance mechanisms in TNBC has led to an increasing focus on mitochondrial metabolism. Altered mitochondrial dynamics, such as changes in oxidative phosphorylation and shifts in tricarboxylic acid (TCA) cycle intermediates, are believed to contribute to reduced chemotherapy sensitivity [114]. Inhibiting ATP production by blocking pyruvate entry into mitochondria restores sensitivity to chemotherapy in drug-resistant breast cancer cells [115]. By targeting mitochondrial pyruvate metabolism, we can potentially reverse drug resistance in TNBC, making it a promising strategy for improving chemotherapy effectiveness.

Furthermore, modulating nicotinamide adenine dinucleotide (NAD) synthesis also influences tumor cell metabolism. For instance, FK886, an inhibitor of nicotinamide-phosphate ribosyltransferase, has demonstrated notable anti-tumor activity in breast cancer cell lines. However, its clinical application is limited due to the development of drug resistance [116]. Studies suggest that mitochondrial re-adaptation during tumor cell metabolism, particularly through pyruvate and succinate depletion, contributes to mitochondrial biogenesis and quality control, thereby enabling the persistence of drug resistance [117]. The persistence of drug resistance continues to drive the search for novel therapies. Recent studies have shown that inhibiting key metabolic pathways with specific inhibitors—such as 2-deoxyglucose,

6-aminonicotinamide, and doxycycline—can target glycolysis, the pentose phosphate pathway, and mitochondrial metabolism [118]. The combination of these inhibitors has shown better anti-cancer potential than using them individually, providing new hope for breast cancer treatment. The use of combination therapies targeting multiple aspects of tumor cell metabolism offers the possibility of overcoming drug resistance, thus improving the effectiveness of chemotherapy.

Aside from conventional drugs targeting tumor cell metabolism, short-term starvation has emerged as a key strategy for influencing TNBC. Pre-treatment starvation before chemotherapy has been shown to enhance cell death and elevate ROS levels [119]. This effect may be attributed to increased DNA damage associated with mitochondrial respiration in TNBC cells, which exhibit altered metabolic profiles. This approach is not only clinically feasible but also holds promise in improving the efficacy of chemotherapy by overcoming resistance in TNBC.

Perspectives

Breast cancer remains one of the most prevalent diseases in clinical practice today, posing significant challenges in treatment due to its complex pathological subtypes, susceptibility to distant metastasis, and the development of drug resistance. Understanding the pathophysiological mechanisms underlying breast cancer and identifying novel therapeutic targets are critical. A review of existing literature highlights the pivotal role of mitochondria in the pathogenesis of breast cancer. Mitochondrial dysfunction, which is primarily driven by factors such as abnormal mtDNA expression, altered copy number, MQC system imbalances, and metabolic disorders, significantly impacts cancer cell proliferation and apoptosis. These findings provide robust evidence supporting the role of mitochondrial dysfunction in breast cancer development, metastasis, and drug resistance. However, breast cancer is a multifactorial disease, and recovery depends on a variety of factors. Glycolysis and oxidative phosphorylation, processes involving mitochondria, are the primary mechanisms through which cells obtain energy. Many of the mechanisms by which mitochondria contribute to breast cancer progression can be traced back to issues of energy acquisition. Addressing metabolic reprogramming in tumors may become the next frontier of research, with new discoveries paving the way for novel therapeutic strategies.

Ultimately, all etiological discoveries aim to improve treatment outcomes. The development of mitochondria-targeted drugs has already shown promising results in preclinical trials, and these therapies—including small molecule inhibitors, chemical drugs, and Chinese herbal medicines—offer broad therapeutic potential, either alone or in combination, by inhibiting cancer cell proliferation or promoting apoptosis. Notably, the development of novel nano delivery platforms combined with chemical-physical technologies is helping to overcome the challenges of drug resistance and targeting in breast cancer treatment. However, more in-depth in vitro and in vivo studies are needed to advance clinical trials and provide further evidence for mitochondrial-targeted therapies in breast cancer treatment.

Conclusion

Mitochondria play a crucial role in various subtypes of breast cancer. This review highlights recent studies on mitochondrial dysfunction in breast cancer, emphasizing the pivotal roles of mtDNA, MQC systems, and metabolic processes in the disease's pathogenesis. Additionally, the review provides an overview of the current drugs that target mitochondria for breast cancer treatment, both in vitro and in vivo. These insights will aid in the development of novel strategies and offer a better understanding of diagnostic, therapeutic, and prognostic approaches for different subtypes of breast cancer.

Abbreviations

ER+	Estrogen receptor
PR+	Progesterone receptor
HER2+	Human epidermal receptor2
MtDNA	Mitochondrial DNA
ATP	Adenosine triphosphate
ROS	Reactive oxygen species
MQC	Mitochondrial quality control
siRNA	Small interfering RNA
TAMs	Tumor-associated macrophages
TNBC	Triple-negative breast cancer
PYCR3	Pyrroline-5-carboxylate reductase 3
NOX4	NADPH oxidase 4
DRP1	Dynamin-related protein 1
MFN2	Mitofusin 2
OXPHOS	Oxidative phosphorylation
mdivi-1	Mitochondrial division inhibitor
TAM	Tamoxifen
MFN1	Mitofusin 1
PINK1	PTEN induced putative kinase 1
MUC1	Mucinucin 1
mTOR	Mammalian target of rapamycin
SIRT1	Sirtuin-1
VDAC1	Voltage-dependent anion channel 1
miRNAs	Micrornas
DYNLT1	Dynein light chain tctex-type 1
IMMT	Endosomal mitochondrial protein
CAF	Cancer-associated fibroblasts
α-KG	Alpha-ketoglutarate
CKMT1	Mitochondrial creatine kinase
DHCR7	7-Dehydrocholesterol reductase
PHD2	Prolyl hydroxylase
AMPKα	AMP-activated protein kinaseα
GYS1	Glycogen synthase 1
RGCC	Response gene to complement 32 protein
BA	Bruceine A
SRF	Sorafenib
ATO	Atovaquone
BSA	Serum albumin
GPX4	Glutathione peroxidase 4
LND	Lonidamine

MMP	Mitochondrial membrane potential
COMET	Combinatorial Organelle Mitochondrial Endoplasmic Reticulum Therapy
RAGE	Receptor of advanced glycation end products
NF-Kb	Nuclear factor kappa-B
TCA	Tricarboxylic acid
NAD	Nicotinamide adenine dinucleotide

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A.H. and H.X. conceptualized the project and wrote the manuscript. T.X., L.X. and H.Y. revised the manuscript. Z.C. and A.M. provided technical guidance. J.Y. supplied funds support. All authors read and approved the final manuscript. Co-first authors are ranked in the order in which they participated in the experiment. All authors reviewed the manuscript and discussed the work.

Declarations

Conflict of interest
The authors declare that they have no conflict of interest.

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