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REVIEW

The role of mitochondria in tumor metastasis and advances in mitochondria-targeted cancer therapy

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Abstract

Mitochondria are central actors in diverse physiological phenomena ranging from energy metabolism to stress signaling and immune modulation. Accumulating scientific evidence points to the critical involvement of specific mitochondrial-associated events, including mitochondrial quality control, intercellular mitochondrial transfer, and mitochondrial genetics, in potentiating the metastatic cascade of neoplastic cells. Furthermore, numerous recent studies have consistently emphasized the highly significant role mitochondria play in coordinating the regulation of tumor-infiltrating immune cells and immunotherapeutic interventions. This review provides a comprehensive and rigorous scholarly investigation of this subject matter, exploring the intricate mechanisms by which mitochondria contribute to tumor metastasis and examining the progress of mitochondria-targeted cancer therapies.

Keywords Tumor metastasis · Metabolism · Mitophagy · Mitochondrial genetics · Mitochondria transfer · Immunotherapy

1 Introduction

Metastasis, the growth of cancer cells in organs far from their origin, is the ultimate and deadliest manifestation of cancer [1]. The vast majority of cancer patients die from metastatic disease, not the primary tumor [2]. The mechanism of tumor metastasis is still being explored, and a number of core issues remain to be resolved. The mainstream consensus now holds that metastasis is a multistep cascade process that requires cancer cells to leave their primary site, circulate in the bloodstream, withstand pressure in the blood vessels, adapt to a new cellular environment at the secondary site, and escape a deadly battle with immune cells [3]. In addition, factors secreted by the primary tumor are thought to facilitate tumor colonization by creating a pre-metastatic niche (PMN) before the tumor cells reach the target organ [2]. Currently, there are limited treatment options for metastatic diseases, and systemic treatments are mainly used, including chemotherapy, targeted therapy, and immunotherapy [4]. Although these therapies have achieved ideal tumor control in some cases with tumor metastasis, the effects are unsatisfactory for a large number of patients, and some are even completely ineffective [5, 6]. Macrometastatic or clinical stage IV disease remains largely incurable, with 5-year survival rates ranging from 5 to 30% [7]. Therefore, prevention of metastasis is considered critical to successful cancer treatment [6]. However, many preclinical and clinical studies have struggled to achieve clinical translation due to a lack of deep understanding of metastatic signaling pathways and the difficulty in assessing whether targeting metastatic pathways would interfere with normal homeostasis [8]. Further

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exploration of the underlying mechanisms of metastasis and the key drivers of tumor progression is needed to develop novel and effective anti-metastatic therapies.

In recent years, researches on tumor metastasis have received increasing attention at the organelle level (e.g., endoplasmic reticulum (ER) [9], lysosomes [10], ribosomes [11]). Organelles are sub-structural units with specific functions in cells, which are closely related to the development of tumors and other diseases [12]. Organelle-targeted therapies have been reported to effectively improve the precision killing of tumor cells while strictly controlling side effects [12]. Among them, mitochondria represent a promising organelle target for eradicating cancer cells as they are found to be associated with multiple hallmarks of cancer [13–15]. The engagement of active mechanisms of mitochondrial quality control can prevent the accumulation of defective mitochondria in human cancers by selectively degrading superfluous or damaged mitochondria, thereby meeting the metabolic demands of the cells [16, 17]. Moreover, cancer cells acquire mitochondria from neighboring cells, not only to repopulate the intact mitochondrial pool but also to gain benefits in terms of tumor malignancy, such as increased proliferation rate, enhanced invasive and metastatic capabilities, and resistance to chemotherapy [18]. Besides, variations in the mitochondrial DNA (mtDNA), including single nucleotide polymorphisms and mutations, can lead to distinctions in metastatic susceptibilities among different cancer histotypes or patient groups [19]. In addition to the direct effects on tumors, mitochondria have been demonstrated to indirectly mediate tumor progression via the regulation of immune cell metabolism and activation in the tumor microenvironment (TME) [20]. Currently, an increasing number of basic researches and clinical trials are being carried out to further clarify the role and mechanism of mitochondria-mediated tumor progression and explore the potential of using mitochondria as a target to inhibit tumor proliferation and metastasis [21, 22].

In this paper, we aim to comprehensively review the role of mitochondria in tumor metastasis and the underlying mechanisms, focusing on their multifaceted physiological properties and functions. Additionally, we also elaborate on the progress of antitumor therapy targeting mitochondria. This article will shed light on the potential of mitochondria-targeted interventions in the management of cancer and promote further exploration of this promising research field.

2 Tumor metastasis

Cancer is a major social, public health and economic problem in the twenty-first century [23]. Cancer metastasis is the main cause of the high mortality rate in cancer patients and a clinical challenge faced by oncologists [1]. According to statistics, up to 63% of different cancers will develop metastasis [24], and more than 80% of cancer patients die from metastatic cancer [25]. Local surgery, radiation, and systemic approaches including chemotherapy, targeted therapy, and immunotherapy are currently the mainstay of metastasis prevention and treatment and have a certain effect on reducing the metastatic tumor mass [5]. Therapeutic goals are the prevention of an initial metastasis in high-risk patients, shrinkage of established lesions, and inhibition of additional metastases in patients with limited disease [26]. Currently, chemotherapy remains the backbone of medical therapy, and with the use of immune checkpoint inhibitors (ICIs), kinase inhibitors (e.g., tyrosine kinase inhibitors), and antibody–drug conjugates (e.g., in $Her2^+$ breast cancer), overall survival has shown significant improvement [7, 27, 28]. Despite these advances, mortality rates have stagnated or risen for several malignancies, including pancreatic cancer, liver cancer, uterine cancer, and some sarcomas, and the vast majority of patients with *de novo* metastatic cancers of any type still die within 5 years of their diagnosis [5]. Improvements in current treatment options remain challenging in significantly changing the poor prognosis of metastatic cancer, underscoring the need for more innovative and effective strategies to combat this deadly disease.

Metastasis is a dynamic, multifaceted process during which cancer cells become resistant to programmed cell death, stimulate angiogenesis, undergo epithelial-mesenchymal transition (EMT), enter neoangiogenic capillaries (intravasation), survive in the bloodstream, evade the immune system, and establish cancerous growths in distant organs [1, 29]. In the initial stages of fighting anoikis (programmed cell death induced by detachment from the stroma), cancer cells attain resistance by suppressing oxidative phosphorylation (OXPHOS) and minimizing reactive oxygen species (ROS) production [30]. Newly formed blood vessels in the tumor are malformed, hyperplastic, branched, highly permeable, and leaky, allowing tumor cells to escape from the primary site and impeding the proper function of immune cells [31–33]. During the intravasation, EMT is activated to facilitate tumor cell detachment and entry into blood or lymphatic vessels [30]. In the context of EMT, transcription factors like HIF-1 and Snail augment the antioxidant capacity of cancer cells, enabling them to withstand oxidative stress post-detachment [34, 35]. Once tumor cells enter the vasculature by intravasation, they are usually destroyed by shear stress or immune surveillance [36, 37]. To avoid this, these cancer cells bind to circulating platelets, which enables them to withstand shear stress and protect them from attack by natural killer cells and T cells [38]. Furthermore, cancer cells are able to prevent antigen presentation by downregulating the expression of the major histocompatibility complex (MHC), allowing them to evade immune surveillance [39]. The metabolism of tumor cells adapts yet, relying on elevated PGC-1α expression to enhance mitochondrial function and ATP production to sustain their energy demands and bolster their invasive potential [40].

To establish metastatic lesions, cancer cells must undergo a complex process of extravasation, including adhesion to endothelial cells at the secondary sites, modulation of the endothelial barrier, and trans-endothelial migration into the underlying tissues [41]. Most of the extravasated cancer cells remain as single cells or form small clusters and become dormant due to the lack of growth factor signals, the actions of metastasis suppressor genes, the lack of activated angiogenic switches at the secondary sites, and the presence of immunological factors [42–44]. When awakened from dormancy, the cancer cells can initiate growth to form macrometastases and interact with the microenvironment to establish a pre-metastatic niche [29, 45].

Given this era of rapid progress in novel therapeutic modalities, multiple opportunities are under investigation that may have a transformative impact on cancer mortality [46]. Multiple agents that target metastatic pathways and endpoints are also being incorporated into development, but still face the problem of preclinical trials meeting expectations but poor or insignificant clinical outcomes [26]. Denosumab, a humanized monoclonal antibody that binds receptor activator of NF-κB ligand (RANKL; also known as TNFSF11), was reported to interrupt the bone metastasis colonization in patients with breast and prostate cancer, thereby delaying the progression of bone metastasis, but it did not significantly improve overall survival [47, 48]. Cilengitide, an αvβ3 and αvβ5 integrin-targeted anti-angiogenic small molecule that affect tumor angiogenesis, viability, invasion, and colonization by inhibiting tumor cell adhesion to the ECM [49], has shown promise in preclinical studies to prevent metastasis [50–52], but failed to show significant clinical activity in phase II trials against several metastatic cancers, possibly due to its short *in vivo* half-life [53–55].

With the rapid and intensive development of research and technology in biology, medicine, and materials science, organelle-targeting strategies hold great potential for next-generation cancer therapies and have emerged as a major approach to personalized cancer treatment [12]. Among the various subcellular structures, mitochondria have attracted much attention due to their unique functions and central role in cellular metabolism [12, 56]. Mitochondria supply energy and regulate redox homeostasis, oncogenic signaling, innate immunity, and apoptosis [57–59]. Therefore, extensive researches are needed to clarify the role and underlying mechanism of mitochondria in tumor metastasis, thereby promoting the development of mitochondria-targeted therapies for tumor metastasis.

3 Mitochondria

Mitochondria are maternally inherited, semiautonomous organelles that originated from the endosymbiotic process of phagocytosis of Proteobacteria by eukaryotic progenitor cells [60]. Mitochondria consist of four compartments: outer mitochondrial membrane (OMM), intermembrane space, inner mitochondrial membrane (IMM), and matrix [61]. The mitochondrial IM possesses a several-fold larger surface than the OM, resulting in an invagination of cristae membranes that harbor the oxidative phosphorylation (OXPHOS) system, including the respiratory complexes I to IV and the F_1F_0-ATP synthase for the production of ATP [62]. Moreover, mitochondria contain a 16 kb circular genome, known as mitochondrial DNA (mtDNA), which encodes tRNAs, rRNAs, and intramembrane proteins necessary for respiration [63].

Bioenergetics, signal transduction, and biosynthesis are three essential functions of mitochondria [64]. Cells consume fuels such as sugars, amino acids, and fatty acids, which are metabolized and shuttled into the tricarboxylic acid (TCA) cycle, a central metabolic pathway located in the mitochondrial matrix [65]. Through iterative oxidations, electrons are stored in the reducing equivalents NADH and FADH2, which deposit electrons into the electron transport chain (ETC) in the IMM and pump protons into the intermembrane space [65, 66]. Protons flow down their electrochemical gradient through F_1F_0-ATP synthase to generate ATP [67]. Seventy years ago, Otto Warburg's observation that cancers acquired the unusual property of taking up and fermenting glucose to lactate in the presence of oxygen (aerobic glycolysis) led him to propose that defective mitochondrial respiration were the potential basis for aerobic glycolysis and cancer [68]. However, researches now suggest that mitochondrial function is essential for cancer cell survival, as the elimination of mtDNA was proved to reduce tumor growth and tumorigenicity [14, 69]. It has been shown that most cancers still preserve mitochondrial function, and some even have high levels of oxidative phosphorylation [70].

The OXPHOS process is also accompanied by the production of the byproduct ROS, which account for almost 90% of the total cellular ROS [71]. Mitochondrial complexes I, II, and III are located within the respiratory chain and are thought to be primarily involved in the production of ROS [72]. OXPHOS is the main process for the generation of unpaired electrons [73, 74], and the interaction of these unpaired electrons with O_2 leads to the production of highly reactive free radical substances (superoxide ions). Superoxide ions readily interconvert into other free radical species such as hydroxide ions (OH^-) and H_2O_2 [73]. To avoid cellular damage caused by ROS, mitochondria develop an antioxidant defense system containing high concentrations of glutathione, Cu/ZnSOD (a variant of superoxide dismutase), and catalase, which removes potentially harmful peroxides produced by SOD [71, 73, 75]. The presence of oxidative stress in the cell indicates an imbalance between the oxidative and antioxidant mechanisms. Abnormally elevated ROS in the mitochondria can activate multiple signaling pathways, such as MAP kinase and HIF, and may become

a driving force in promoting tumorigenesis and development [75, 76]. Despite the progress in relevant researches, the main mechanisms by which ROS are involved in cancer development in a concentration-, spatial-, and time-dependent manner remain insufficiently understood [75].

Mitochondria also participated in a variety of cellular signaling and functional regulation by mediating Ca^{2+} homeostasis through the "Mitochondrial Calcium Uniporter" (MCU) [77]. Calcium influx into mitochondria activates multiple enzymes of the TCA cycle and ETC, which increases NADH and FADH2 production and stimulates ATP synthesis [77, 78]. Deletion of MCU was observed to reduce mitochondrial ROS production, thus reducing HIF-1α levels and impairing metastatic invasiveness [79]. Besides, an excessive mitochondrial Ca^{2+} uptake (Ca^{2+} overload) stimulates the permeability transition pore (PTP) opening and cytochrome C release, activating apoptotic cascade [77]. These Ca^{2+} signals can also activate the phosphatase calcineurin, which dephosphorylates the proapoptotic BH3-only protein Bad [80]. Dephosphorylated Bad then binds to antiapoptotic Bcl-X_L proteins to antagonize its antiapoptotic properties, resulting in the activation of proapoptotic proteins Bax/Bak, mitochondrial outer membrane permeabilization, and thus apoptosis [81]. Targeting the regulation or function of pro-survival BCL-2 family members located in the OMM shows high potential in improving the treatment of many lymphoid malignancies [82, 83].

Mitochondria are the key signaling platform for immune responses [84, 85]. For example, the mitochondrial antiviral-signaling (MAVS) protein is an important platform for antiviral immunity, responding to viral infection and activating immune defense mechanisms such as interferon production [84]. When mitochondria are damaged or ruptured, the released mtDNA serves as endogenous damage-associated molecular patterns (DAMPs) that activate pattern-recognition receptors (PRRs) on the surface of immune cells, which triggers innate immune responses against non-microbially induced inflammation [85]. Mitochondrial signaling and metabolism are also required for the proper activation of T cells, which are central orchestrators of adaptive immune responses [84]. Upon binding of the T cell receptor (TCR) to the MHC, the transcription factor MYC is activated and shifts Naïve T cells to a robust anabolic state by increasing glucose and glutamine uptake, which allows the T cells to meet the metabolic demands necessary for proliferation and induction of an adaptive immune response [86, 87]. Following the ligation of the TCR, mitochondria generate ROS as a necessary signal for the proper activity of the nuclear factor of activated T cells (NFAT) and IL-2 production, both of which contribute to T cell activation [88, 89].

Mitochondria serve as the building blocks of biosynthesis generator, ensuring a balance between the supply and demand of four-carbon and two-carbon units to support the synthesis of a wide range of biomolecules such as amino acids and lipids [90, 91]. Through the TCA cycle and close interaction with other metabolic pathways, mitochondria also generate key intermediates such as citric acids, which are not only involved in cyclic reactions but also transported to the cytoplasm to promote lipid and protein synthesis [92]. Mitochondria are essential in one-carbon metabolism, participating in the synthesis of purines, thymidine, and methionine, emphasizing their importance as a biosynthetic crossroads [93]. Dihydroorotate dehydrogenase (DHODH) in mitochondria is necessary for pyrimidine synthesis and is dependent on the complete function of the respiratory chain [94]. The DHODH-CoQH2 system clears lipid radicals by catalyzing the conversion of dihydroorotate (DHO) to orotate (OA) and refreshing the antioxidant CoQH2, thereby preventing lipid peroxidation and ferroptosis [95]. It has been shown that targeted inhibition of DHODH can contribute to tumor cell ferroptosis [96]. Taken together, mitochondria maintain a complex network of cellular metabolism, growth, and survival by integrating energy metabolism, signaling, and biosynthesis.

In addition to the basic mitochondrial functions, many mitochondrial biological properties (quality control, transfer, genetics) have also been found to engage in and influence tumor metastasis (Fig. 1). Since the discovery of the Warburg phenomenon in 1924, research progress related to mitochondria has accelerated [97], from the initial detection of mitophagy in mammalian cells in 1966 [98] to the detection of the PINK1-Parkin pathway involved in mitochondria elimination in 2010 [99]. In 1998, Polyak published the first description of mtDNA mutations in cancer and started a wave of research into mtDNA [100]. In 2000, mitochondrial complex II mutations were first discovered in tumors, which led to the exploration of the relationship between mitochondrial gene mutations and tumors [101]. Intercellular mitochondrial transfer was first observed in 2006 [102]. Nanotube-mediated mitochondrial transfer from immune cells to tumor cells was detected in 2022 [103]. Mitochondrial RNA modification-mediated metabolic plasticity was also identified in 2022 [104]. Further frontier studies on the relationship between mitochondria and tumor metastasis are currently underway and will contribute to a deeper understanding of the underlying mechanisms in the near future.

4 The role of mitochondria in tumor metastasis

Based on the fundamental physiological functions of mitochondria outlined in the above section, this section will further reveal the fine mechanisms of mitochondrial quality control in mediating tumor metastasis, the influence of

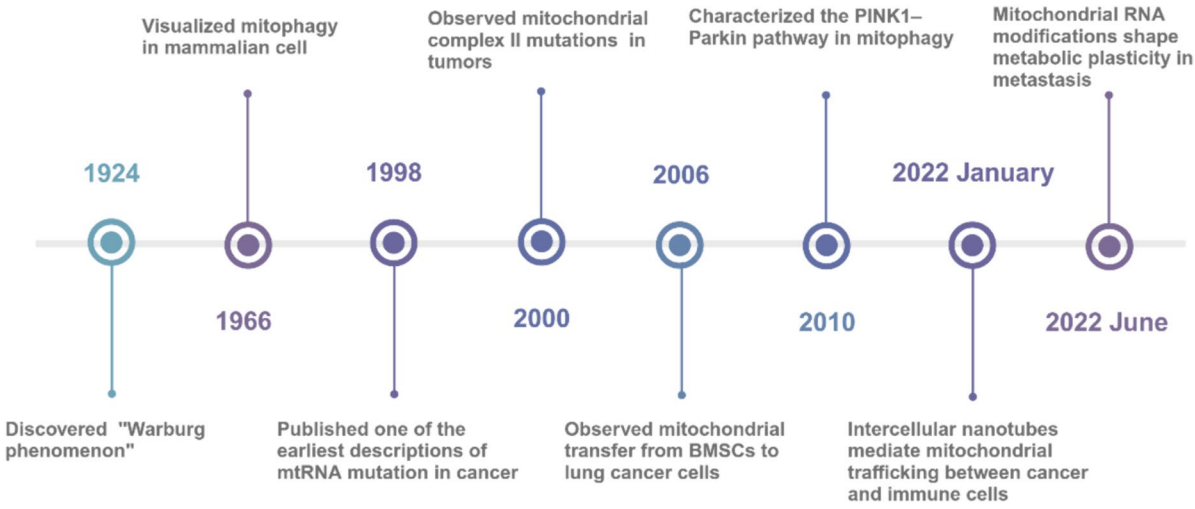

Fig. 1 The timeline of several important discoveries in mitochondria-related research

unique genetic features of mitochondria and the phenomenon of mitochondrial transfer on tumor progression, and the deep involvement of mitochondria in reshaping the TME. Intensive researches on mitochondria in tumor metastasis help provide a scientific basis and innovative ideas for the development of novel antitumor metastasis strategies.

4.1 Mitochondrial quality control in metastasis

Mitochondrial quality control (MQC) is an integrated network that monitors mitochondrial quality and is an endogenous cellular protective program that is critical for maintaining mitochondrial homeostasis and function [105]. In response to mitochondrial damage, the MQC system, which regulates mitochondrial fission/fusion, mitophagy, and biogenesis, is activated to repair or remove structurally defective mitochondria in order to maintain mitochondrial function and ATP production [106]. Mitochondrial dysfunction will lead to the progression of metabolic or neurological diseases and even cancer [107–109].

4.1.1 Mitophagy in metastasis

Cells generally employ mitophagy to eliminate dysfunctional mitochondria and avoid increased ROS in response to external stresses, including hypoxia and nutrient deprivation [110]. At the physiological level, ROS are regulated by antioxidant mechanisms. Physiological disturbances lead to excessive production of ROS, which cause oxidative damage to mitochondrial proteins, lipids, and DNA, resulting in mitochondrial damage. Subsequently, mitochondrial damage leads to changes in mitochondrial membrane potential (MMP) that stimulate mitophagy, which then eliminates dysfunctional or excess mitochondria to protect the cells from the oxidative stress [111]. The turnover of mitochondria via mitophagy is dependent on the activity of mitochondrial cargo receptors (MCRs), including BNIP3, BNIP3L (NIX), FUNDC1, and others, as well as mitochondrial proteins that serve as substrates for PINK1/Parkin-mediated ubiquitination [112]. These MCRs link mitochondria to autophagosomes through interactions with members of the LC3/GABARAP family. Dysregulation of mitophagy results in the accumulation of damaged mitochondria, which significantly contributes to carcinogenesis and tumor progression [113] (Table 1).

PINK1/Parkin-dependent mitophagy is the major mechanism by which cells maintain mitochondrial function and metabolic homeostasis by removing depolarized mitochondria, preventing Warburg metabolism and the effects of excess ROS [130]. In KRAS-driven PDAC, the loss of Parkin or PINK1 increases mitochondrial iron accumulation, which subsequently leads to the HIF-1α-dependent glycolysis and AIM2-dependent inflammasome activation, resulting in tumorigenesis and metastasis [114]. Parkin also promotes HIF-1α ubiquitination to inhibit breast cancer metastasis [116]. For established tumors, mitophagy has been demonstrated to be required for stress adaptation and survival [131]. Stomatin-like protein 2 (STOML2) amplifies mitophagy by stabilizing PINK1 under cellular stress, thereby promoting hepatocellular carcinoma (HCC) growth and metastasis [115].

BNIP3 and BNIP3L function as key stress-inducible MCRs in tumor metastasis through multiple pathways. BNIP3 expression upregulation causes mitochondrial dysfunction and ATP deficiency through excessive mitophagy, ultimately inhibiting HCC migration and metastasis [119]. In the invasive and metastatic stages of cancer,

Table 1 The role of mitophagy/mitochondria-associated protein in tumor metastasis and the related mechanisms

Protein	Alteration	Cancer	Mechanism	Metastasis	Ref
PINK1/Parkin	Loss	PDAC	Induced mitochondrial iron-dependent immune metabolism disorder	↑	[114]
	Upregulation	HCC	Amplified mitophagy potentiated by STOML2	↑	[115]
	Downregulation	Breast cancer	Upregulated HIF-1α expression	↑	[116]
BNIP3/BNIP3L	Loss	TNBC	Increased the production of destructive ROS and further upregulated HIF-1α expression	↑	[117]
	Loss	Pancreatic cancer	Induced the hypermethylation of the BNIP3 promoter	↑	[118]
	Loss	HCC	Limited JNK phosphorylation and prevented intracellular calcium overload	↑	[119]
FUNDC 1	Loss	Prostate cancer	Triggered mitochondrial repositioning	↑	[120]
		Glioblastoma		↑	
	Upregulation	Breast cancer	Promoted $Ca2^{+}$ influx into the nucleus and activated the oncogene BMI1	↑	[121]
DRP1	Overexpression	Pancreatic cancer	Promoted mitochondrial fragmentation, shifted metabolism to glycolysis, increased glucose uptake and lactate production	↑	[122]
		HCC	Increased mitochondrial fragmentation, promoted Ca2 + /CaMKII/ERK/FAK pathway for faster focal adhesion turnover	↑	[123]
MiD49	Overexpression	Ovarian cancer	Increased mitochondrial ROS production and subsequently activation of AKT/mTOR signaling pathway	↑	[124]
		Pancreatic cancer	Increased ROS production inducing tumor cell death	↑	[125]
SNPH	Loss	Breast cancer Prostate cancer	Exhibited higher oxidative stress, reduced cell proliferation, and increased cell motility	↑	[126]
OPA1	Loss	Melanoma Breast cancer	Increased cytosolic Ca2 + , activated NF-κB, and thus reduced tumor angiogenesis	↑	[127]
MTP18	Overexpression	HCC	Promoted mitochondrial fission and ROS production	↑	[128]
MARCH5	Overexpression	Breast cancer	Promoted mitochondrial fission and ROS production	↑	[129]

hypermethylation of the BNIP3 promoter frequently leads to the inactivation of BNIP3 [132, 133]. Loss of BNIP3 may contribute to hypoxia-induced cell death resistance [118] and upregulated expression of genes related to glycolysis and angiogenesis [117], which increases tumor invasiveness and chemoresistance [117, 133]. However, BNIP3L ablation was found to mediate metabolic transformation and reduce damaged ROS production, thereby significantly delaying cancer progression [134]. Additionally, previous study showed that BNIP3- and BNIP3L-induced mitophagy increased the number of memory NK cells and promoted their survival, thereby affecting tumor growth and metastasis [135]. Further studies are needed to clarify the complex role of BNIP3/BNIP3L in mediating tumor progression.

FUNDC1 is another hypoxia-induced mitophagy receptor [136]. FUNDC1-dependent mitophagy antagonizes oncogene SRC-driven tumor cell migration and invasion. In prostate cancer and glioblastoma, silencing of FUNDC1 was observed to promote the recruitment of the Ser616-phosphorylated DRP1, resulting in increased mitochondria fission and redistribution to the cortical cytoskeleton. Repositioning of mitochondria promotes cell migration and invasion [120]. Notably, elevated FUNDC1 levels were also reported to enhance the proliferation and metastasis of tumor cells by activating the transcription of the oncogene BMI1 via Ca^{2+} influx into the nucleus [121]. In conclusion, as a central component of the cellular MQC system, mitophagy contributes to the maintenance of cell function.

4.1.2 Mitochondrial dynamics in metastasis

Mitochondrial dynamics is the process of mitochondrial fusion and fission that determines the shape, mass, and number of mitochondria [137]. Mitochondrial dynamics is regulated by a number of highly conserved large guanosine triphosphatases (GTPases) [137]. Fusion of the outer mitochondrial membrane (OMM) is mediated by mitofusin 1 and mitofusin 2 (Mfn1 and Mfn2), while inner mitochondrial membrane (IMM) fusion is regulated by optic atrophy 1 (OPA1) [138]. Mitochondrial fission is controlled by dynamin-related protein 1 (DRP1) [138]. Oncogenic signals that drive hyperproliferation, increase intracellular stress, and limit nutrient supply are capable of altering the bioenergetic and biosynthetic requirements of cancer cells [138, 139]. Consequently, mitochondrial function and shape rapidly adapt to these adverse conditions to support cancer cell proliferation and escape activation of the cell death program [139].

The phenomenon of mitochondrial fission is considered to be a key factor in promoting tumor progression [139].

Studies have shown that the expression levels of fission-promoting proteins (e.g., DRP1 [140], MFF [141], FIS1 [142], MiD49 [143]) are increased in a variety of cancers compared to normal tissues, which is closely related to the enhanced metastatic potential. DRP1 expression increases with breast cancer progression, and mitochondria become more fragmented in metastatic breast cancer cells [140]. By inhibiting DRP1, the metastatic ability of these cells could be significantly reduced, whereas overexpression of Mfn1 or Mfn2 showed the opposite effect. Similarly, high expression of DRP1 with low expression of Mfn1 in HCC predicts poorer survival, and DRP1 is critical for the formation of intrahepatic and lung metastases [123].

Mitochondrial fission affects tumor metastasis through complex multi-pathway mechanisms that involve metabolic reprogramming [144], $Ca2^{+}$-driven motility [123], and lamellipodia formation [140]. Specifically, changes in mitochondrial morphology promote a metabolic shift from OXPHOS to glycolysis [122]. DRP1 overexpression-induced mitochondrial fragmentation promotes increased glucose uptake and lactate production in pancreatic cancer, as well as MiD49 overexpression affects lipid synthesis in ovarian cancer, both of which contribute to tumor progression by affecting energy metabolism [122, 124]. In addition, mitochondrial fission promotes faster focal adhesion turnover and the increased number of membrane protrusions through the Ca^{2+}/CaMKII/ERK/FAK pathway, which facilitates tumor cell migration [123, 140]. Previous study revealed that mitochondrial subcellular localization and their dynamic transport were regulated by multiple proteins, such as syntaphilin (SNPH), a cytoskeletal regulator of mitochondrial motility, which negatively regulated the metastatic potential of tumor cells by controlling the distribution of mitochondria [145]. Depletion of SNPH increases mitochondrial fission and fusion events and thereby enhances the invasive capacity of tumor cells, which could be significantly abrogated by the deletion of Mfn1 or Mfn2 [126, 146].

In addition to focusing on the importance of tumor cell–intrinsic mitochondrial morphology changes in metastasis, recent studies have also shifted attention to endothelial cells in the TME [127]. Loss of OPA1 leads to increased cytoplasmic Ca2 +, activation of NF-κB, and reduced expression of key angiogenic genes, thereby significantly reducing tumor growth and metastasis [127]. Indeed, silencing of Mfn1 or Mfn2 fragments mitochondria as does silencing of OPA 1, but has no effect on endothelial cell motility, proliferation, or growth, which is in contrast to the findings in HCC cells where mitochondrial fragmentation caused by Mfn1 deficiency actually increased migration and invasion capacity via $Ca2^{+}$-dependent signaling pathways [123]. Thus, mitochondrial fission has different outcomes depending on the cell type in which the mitochondria are fragmented as well as the proteins that cause mitochondrial fission. Future study is needed to fully elucidate the mechanisms by which mitochondrial fission/fusion in non-tumorigenic cells affects tumor metastasis.

ROS play a dual role in tumor biology, both promoting and inhibiting tumor development, with their effects depending on expression levels, exposure time, and cell types [147–149]. The dynamic balance of mitochondrial fission/fusion is regulated by proteins such as MTP18 [128], MARCH5 [129], and MiD49 [124, 143], which affect ROS production and thus regulate the metastatic potential of different cancers. MTP18 promotes mitochondrial fission and ROS production in HCC, accelerating metastasis and leading to poor prognosis [128]. MARCH5 was found to promote tumor progression through a similar mechanism in breast cancer [129]. ROS induced by MiD49 was shown to activate pro-metastatic signaling in ovarian cancer [143] but inhibit metastasis in pancreatic cancer [125], reflecting cell environment dependence. Studies have also revealed that ROS not only act as a consequence of mitochondrial fission but also promote mitochondrial fission in turn, as IDH2 [150] and FUNDC1 [120] deletion was found to drive DRP1-mediated mitochondrial division and cell migration, respectively, by upregulating ROS in prostate cancer. These studies demonstrate a complex interaction between mitochondrial dynamics and ROS that co-regulate multiple metastatic phenotypes in tumors, emphasizing the importance of understanding the mechanism of this interaction for specific cancer types.

4.2 Mitochondrial transfer in metastasis

A flurry of researches in the past decade have revealed that mitochondrial transfer occurs in numerous tissues and this process is involved in both normal physiological processes and disease pathogenesis [60, 151]. Notably, emerging evidence indicates a pivotal role of mitochondrial transfer in tumor progression and metastasis [152]. Mitochondrial transfer between cancer and nonmalignant cells results in the incorporation of either mitochondrial genes or mitochondria themselves into the recipient cells [60, 153], which leads to noteworthy alterations to the biological energy state of the host and significant changes in cellular differentiation and inflammatory processes. Mitochondrial transfer relies on several structures, such as extracellular vesicles (EVs), tunnel nanotubes (TNTs), and gap junctions, among which TNTs are recognized as major intercellular platforms for unidirectional and bidirectional mitochondrial exchange [18].

4.2.1 TNT-mediated mitochondrial transfer

TNTs are thin (70–800 nm wide) membrane tubes connecting remote cells and allowing the transfer of cellular content [154]. Miro proteins control the movement and distribution of mitochondria within and between cells, acting as adaptors

for linking organelles and cytoskeleton-related proteins [155]. The Miro protein encoded by RHOT1 was reported to potentially promote TNT-mediated mitochondrial transfer [156]. In epithelial cancer cells, RHOT1 could function as an intermediary between mitochondria and microtubules, regulating the quantity of anterior-localized mitochondria and thus determining the invasive ability between cells [157]. RHOT1 can regulate cell migration and proliferation by inhibiting the expression of SMAD4 (an effector of RHOT1) in pancreatic cancer [158]. Conversely, SNPH in tumors reduces the efficiency of mitochondrial transfer, while downregulation of SNPH has been shown to enhance mitochondrial transfer to the cortical cytoskeleton, promoting tumor invasion [146].

Investigations of the mechanism of intercellular mitochondrial transfer in solid tumors point to TNTs as the main delivery pathway [159–161]. Stromal cells in the TME have been found to interact with tumor cells through TNT-mediated mitochondrial transfer. Most studies have shown that after receiving stromal cell mitochondria, tumor cells exhibit enhanced chemoresistance, proliferation, and invasion capabilities [154, 162, 163]. Cancer-associated fibroblasts (CAFs) were demonstrated to establish a metabolic symbiosis with prostate cancer (PCa) cells [161]. Lactate released by CAFs affects the affinity of cancer cells for external mitochondria and the ability of cancer cells to hijack CAF-derived functional mitochondria, thereby promoting cancer invasion [161]. Additionally, endothelial cells and macrophages have been observed to transfer mitochondria to ovarian and breast cancer cells, respectively, resulting in enhanced tumor invasion [159, 164]. However, our recent study has shown that mitochondria transferred from osteocytes to cancer cells would trigger cGAS/STING-mediated antitumor responses, thereby inhibiting the progression of bone metastasis [165]. The ultimate influence of mitochondrial transfer on tumor metastasis and its related mechanisms remains to be further investigated (Fig. 2).

4.2.2 EV-mediated mitochondrial transfer

EVs, including exosomes, microvesicles, and apoptotic bodies, are cell-secreted nanoscale, bilayer-structured vesicles that can carry a variety of lipids, proteins, RNAs, miRNAs, and mitochondria [166]. EV-mediated mitochondrial transfer can also occur within cancer cells or between cancer cells and other cells and is involved in regulating the tumor microenvironment and metastasis [167]. For example, mtDNA-rich EVs from breast cancer cells increase the expression of matrix metalloproteinases and $\alpha_5\beta_1$ integrin to promote metastasis of recipient breast cancer cells under glutamine starvation conditions [168]. Our previous study showed that platelet-derived mitochondria regulated the GSH/GSSG ratio and ROS in recipient tumor cells to promote lung metastasis of osteosarcoma [169]. In addition, EV-mediated mitochondrial delivery also contributes to chemotherapy resistance,

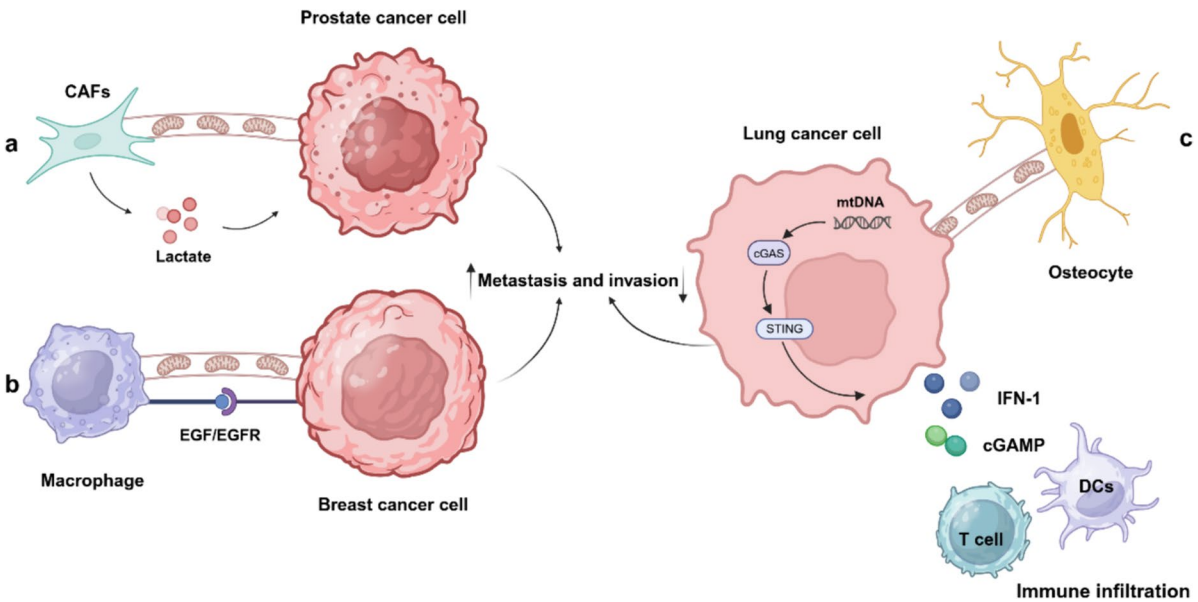

Fig. 2 TNT-dependent mitochondrial transfer between stromal cells and tumor cells influences tumor metastasis and invasion. **a** Lactate released by CAFs enhances the ability of cancer cells to hijack CAF-derived functional mitochondria by forming TNTs. **b** TNTs between macrophages and breast tumor cells were dependent on EGF–EGFR signaling to induce invasive tumor cell morphology. **c** Mitochondria transferred from osteocytes to cancer cells would trigger cGAS/STING-mediated antitumor responses, thereby inhibiting tumor metastasis

thereby promoting tumor progression [170]. EVs released from chemoresistant triple-negative breast cancer cells can promote chemoresistance and tumor progression in chemosensitive triple-negative breast cancer cells by delivering functional mitochondria [171]. Similarly, EV from tumor-activated fibroblasts delivers mitochondria to malignant glioma cells, leading to resistance to radiotherapy and chemotherapy [172].

4.2.3 Gap junction–mediated mitochondrial transfer

The gap junction channel (GJC) is the most direct channel for substance exchange between two adjacent cells and is formed by the docking of their respective hemichannels, which are hollow tubular structures formed in the cell membrane by oligomerization of six connexin subunits [173]. However, mitochondria are apparently unable to be directly transported between cells through GJCs, as the pore size of gap junctions is only 1.5–2 nm [173]. An increasing number of researches revealed the involvement of GJCs in facilitating mitochondrial transfer mediated by TNTs [174]. The inhibition of GJCs interferes with normal communication between TNT connective cells [174]. Connexins, in particular connexin 43 (Cx43) presented in TNT-like structures, play a key role in this process [173, 175]. Knockdown of CX43 in TNTs significantly was reported to affect TNT formation and reduced mitochondrial transfer between mesenchymal stem cells and epithelial cells [176]. In contrast, upregulated Cx43 expression promotes mitochondrial transfer from astrocytes to neurons via TNT-like structures [177]. In glioblastoma, CX43-based GJCs may accelerate TNT formation and mitochondrial transfer by assisting tumor microtubules to contact cells and conduct more signal exchanges, thereby promoting tumor progression [178]. At present, the connection between TNTs and CX43-based GJCs in intercellular communication remains ambiguous and needs further exploration.

4.3 Mitochondrial genetics in metastasis

Due to the tiny size of the mitochondrial genome relative to the nuclear genome, studies on the role of mitochondrial genetics in cancer have been overlooked over the past few decades. Now, mtDNA is well recognized as a crucial regulator of cellular function. MtDNA copy number variants (CNVs) and somatic mutations significantly contribute to cancer initiation, progression, and metastasis [179].

MtDNA CNVs exist in a variety of cancers (Table 2). Compared to those observed in noncancerous tissues, there are varying trends in which the mtDNA copy number increases or decreases across different types of cancer [180–187]. On the one hand, some studies revealed that decreased mtDNA copy number led to tumor metastasis and more aggressive behavior due to the reduced activity of the respiratory enzyme complex [182, 188] and elevated ROS production as well as enhanced antiapoptotic capacity [180, 183–185, 187]. On the other hand, increased mtDNA copy number among pancreatic cancer, head and neck cancer, and esophageal cancer was also found to be correlated with tumor malignancy and suggested enhanced biosynthetic and energetic activity [189–191]. Both increase and decrease in mitochondrial DNA copy number have been reported to promote metastasis in lung and prostate cancers [192–196], suggesting that considerable intertumor and intratumor heterogeneity exist in the spatial distribution of mtDNA [195, 197]. Diverse trends in mtDNA CNVs have also recently been shown to potentially influence tumorigenesis and/or metastasis by modulating mitochondrial biogenesis [179]. Further investigation is required to fully comprehend this phenomenon.

Wild-type and mutant mtDNAs coexist in a heteroplasmic state [206] and are distributed randomly into daughter cells, causing a drift in the proportion of mutated mtDNA toward homoplasmy [184, 207]. The biological impact of mutation depends on the proportion of cells with mutated mtDNA [206, 208]. Somatic mutations are associated with specific cancer types in both protein-coding and noncoding regions of the mitochondrial genome, with a greater frequency of mutations in the D-loop [209, 210]. Somatic mtDNA mutations were reported in 74% of breast cancer patients, most of which (81.5%) were confined to the D-loop [207]. It was also reported that 48% of gastric cancer patients presented somatic mutations in the D-loop region [184]. Through whole-mitochondrial genome analysis of non-small cell lung carcinoma (NSCLC), tumor-specific mutations are widely present throughout the mitochondrial genome [211]. The number and burden of heteroplasmic shifts (variations in allele frequencies greater than 10% between tumors and normal tissues) increased with higher tumor stage or lymph node metastasis [211]. The tumor-specific somatic variants were highly variable in their location and heteroplasmic level, resulting in unique profiles of mitochondrial variants in most tumors, and were maintained during metastasis with some additional mutations [211, 212].

MtDNA alterations resulting from somatic mutations are associated with carcinogenesis and metastasis. A decreased mtDNA amount is frequently observed in osteosarcoma, potentially due to somatic D-loop mutations [213]. Somatic D-loop mutations are also regarded as one of the key factors leading to quantitative changes in mtDNA within Ewing's sarcoma [182]. The data showed a statistically significant association between reduced mtDNA copy number and tumor metastasis in osteosarcoma and Ewing's sarcoma. Nonetheless, increased somatic mtDNA mutations have also

Table 2 Summary of mtDNA CNVs in different cancers

Cancer	MtDNA CNVs	Mechanism	Ref
Gastric cancer	Decrease	Enhanced apoptosis resistance and more leakage of ROS with lower coupling efficiency of the respiratory chain	[184]
HCC		Increased ROS production and Ca^{2+} mobilization and reduced ATP generation	[185]
Breast cancer		Contributed to altered energy metabolism, increased ROS, and an attenuated apoptotic response to anticancer drugs	[183]
Renal cancer		Decreased the content of OXPHOS complexes	[181]
Colorectal cancer		Reduced the dependence of mitochondrial oxidative phosphorylation	[180]
Ewing's sarcoma		Decreased the activity of respiratory enzyme complexes and mitochondrial dysfunction	[182]
AML	Increase	Enhanced mitochondrial complex II and V activity	[198, 199]
Endometrial cancer		Increased mtDNA content and citrate synthase activity stimulated by estrogen	[200]
Pancreatic adenocarcinoma		Promoted the packaging and shedding of the mtDNA cargo through EVs to avoid apoptosis and immune activation	[201]
Head and neck cancer		Inhibited cell proliferation and apoptosis by producing ROS	[190, 202]
Esophageal cancer		Increased bioenergetic capability and interrupted tumor suppressor gene function	[191, 203]
Lung cancer	Decrease	Activated mitochondrial stress-induced calcium signaling	[192–194, 204, 205]
	Increase	Promoted energy metabolism adaption	
Prostatic cancer	Decrease	Decreased MMP and reduced PARP-1 protein levels	[195, 196]
	Increase	Increased the activity of respiratory chain–related enzymes (COX and SDH)	

been associated with tumor progression and metastasis in NSCLC [214], melanoma [215], and prostate cancer [216]. These mtDNA alterations may provide insights into the risk of carcinogenesis and metastasis.

5 Mitochondrial immune regulation in the TME

TME is a complex ecosystem composed of tumor cells, stroma, vasculature, and immune cells, which together form an intricate network of resource acquisition and resource exchange [217]. In the TME, tumor cells drive the differentiation of tissue-resident stromal cells and infiltrating monocytes into CAFs and tumor-associated macrophages (TAMs), while impairing the antitumor effect and survival of T cells, thereby creating an immunosuppressive microenvironment to promote tumor progression [217] (Fig. 3). Mitochondrial metabolic activities in various cell types transcend conventional functions and are intimately involved in a series of transformational events that play important roles in shaping the TME and tumor progression.

5.1 Mitochondrial regulation of T cell

Mitochondria regulate T cell biology by dynamically responding to cellular demands [20]. T cell function and differentiation are influenced by changes in mitochondrial morphology and energy metabolism [218]. T cell activation is intricately dependent on DRP1 and regulated by a series of signaling pathways, including the AMPK [219] and RAS/RAF/ERK [220] pathways. DRP1 can promote the aggregation of mitochondria under TCR clusters on the plasma membrane [221]. Mitochondrial fragmentation accumulated under TCR clusters is necessary for immune synapse (IS) formation [222, 223]. ATP, local calcium buffering, transcription factor activation, and cytokine secretion provided by mitochondrial fragmentation are critical to establish ISs. Upon the binding of the TCR complex to a tumor antigen, a subsequent influx of calcium ions ensues, triggering the release of ROS from the mitochondria [224], which in turn can regulate the secretion of IL-2 and IL-4, essential for the activation and proliferation of $CD8^+$ T cells [225].

Increased mitochondria-mediated intrinsic apoptosis reduces the longevity and number of $CD8^+$ T cells [226]. Under the stimulation of cell stress, apoptosis is initiated, and then the permeability of the mitochondrial membrane increases. Bcl-2 family proteins regulate the release of nucleases and proteases (such as cytochrome c) from mitochondria to form apoptotic bodies, which can trigger subsequent caspase cascade reactions and induce apoptotic degradation [227, 228]. Mitochondria-mediated apoptosis leads to a decreased amount of $CD8^+$ T cells, which inevitably

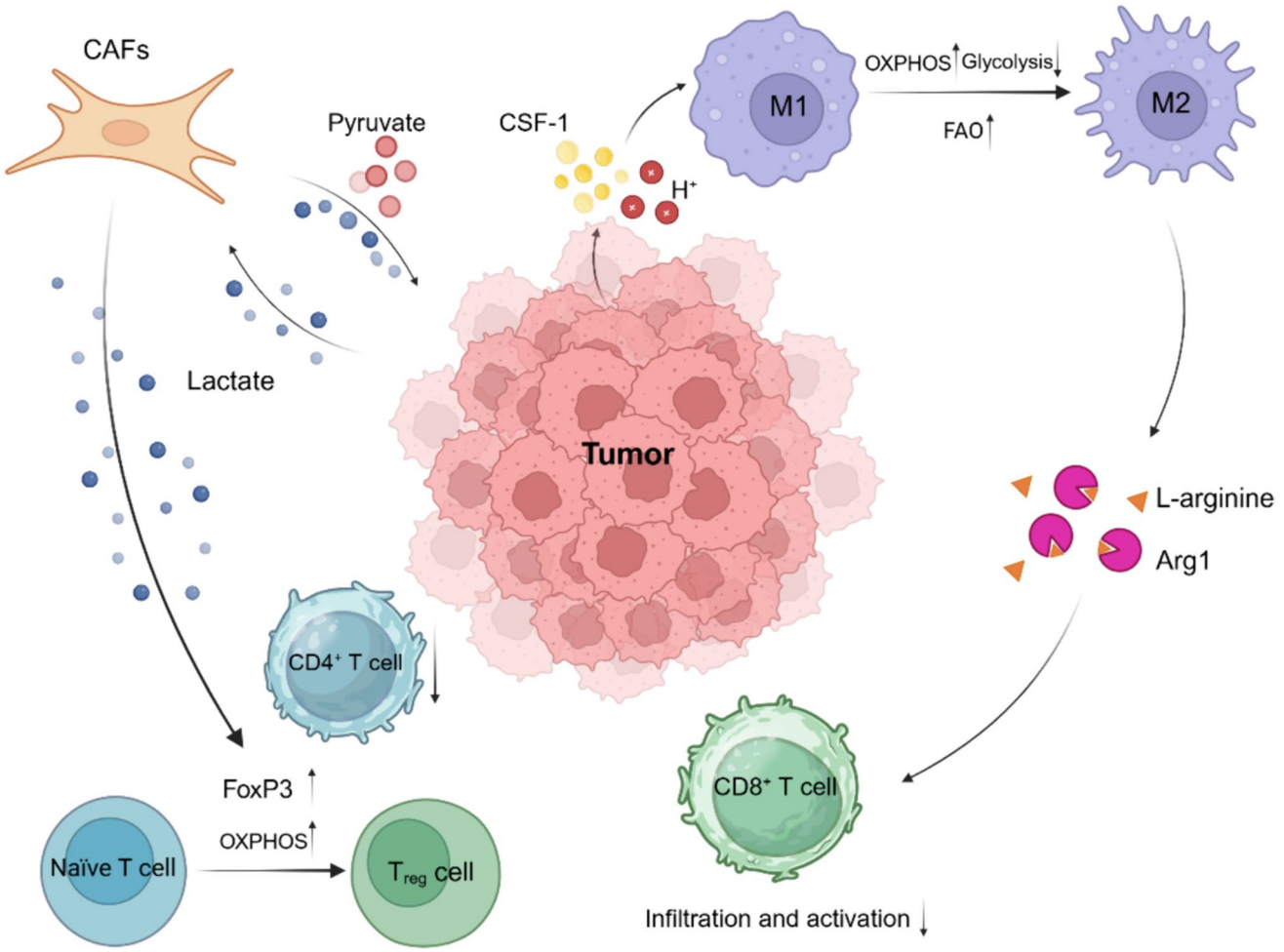

Fig. 3 The interaction of CAFs, TAMs, and T cells in the TME. In the TME, cancer cells undergo aerobic glycolysis, consume large amounts of glucose, produce lactate and H^+ in the TME, and release elevated CSF1, promoting the polarization of M1 macrophages to immunosuppressive M2 macrophages. M2 macrophages can directly and negatively affect effector T cell infiltration and activation within tumors through the expression of ARG1. Glycolytic CAFs secrete lactate and pyruvate to fuel the TCA cycle of malignant cells and support mitochondrial metabolism. Lactate from cancer cells also serves as a fuel source for CAFs, further enhancing its tumor-promoting activity. Glycolytic CAF-secreted lactate directly overcomes immunosurveillance by reducing $CD4^+$ Th1 populations and promoting FoxP3-mediated conversion of Naïve T cells to Tregs

weaken immune surveillance and promote tumor progression [226].

T cells are important effector cells in the host response to malignant cells. However, tumors in general induce an immunosuppressive microenvironment due to biophysical constraints, reduced oxygen saturation, nutrient deprivation, and the abundance of anti-inflammatory molecules [229], which partially impairs the metabolic switch to aerobic glycolysis required for T cell activation, thereby limiting the ability of T cells to exert antitumor effects [230]. T cells in the TME typically display exhausted (T_{ex}) phenotypes, characterized by the expression of inhibitory receptors such as PD-1, LAG3, TIM3, and TIGIT, as well as reduced effector function and proliferative capacity [231]. T_{ex} cells exhibit marked alterations in mitochondrial abundance, dynamics, membrane potential, and production of OXPHOS and ROS. The reduction in mitochondrial mass in T_{ex} cells is primarily due to defective expression of PGC-1α (an important driver of mitochondrial biogenesis), and overexpression of PGC-1α can rescue their antitumor function [232, 233]. Treatment with antioxidants or nicotinamide riboside (promoter of mitophagy) was demonstrated to restore $CD8^+$ T_{ex} cell antitumor activity by promoting cristae expansion, reducing ETC efficiency, and upregulating aerobic glycolysis [234–236]. Binding of the programmed death-1 (PD-1) receptor to its ligands transduces inhibitory signals that promote the exhaustion of activated T cells [237]. PD-1 blockade was shown to improve the shortened mitochondrial cristae length and reduced membrane potential in tumor-infiltrating PD-1^+ $CD8^+$ T lymphocytes from NSCLC patients [238].

Studies have demonstrated that there exist multistage developmental hierarchies among classically defined PD-1$^+$ CD8$^+$ T_{ex} cells [239]. Progenitors, intermediate cells, and terminally exhausted T cells are defined by the expression of the transcription factors Tcf-1, T-bet, and TOX, respectively [239]. It is currently believed that sustained activation of NFAT due to disturbed ROS production may enhance TOX expression, while the increased ROS levels are associated with decreased Tcf-1 expression [236, 240, 241]. Mitochondrial dysfunction at the progenitor cell stage due to antigen persistence may lead to increased oxidative stress, which may have an opposite effect on TOX and Tcf-1 expression [236, 241]. Thus, the reversal of mitochondrial dysfunction at the progenitor cell stage may prevent the differentiation of CD8$^+$ T_{ex} cells.

5.2 Mitochondrial regulation of TAMs

TAMs comprise about 50% of the immune cells in the TME and are able to maintain an activated state under various unfavorable environmental factors, such as low nutrition, acidic pH, hypoxia, and oncometabolite [234, 242]. The metabolism and function of TAM subpopulations may also be differentially affected due to these environmental factors in the TME and the uneven distribution of these factors within the tumor [243]. In general, M1-like macrophages rely mainly on glycolysis, while M2-like macrophages depend on OXPHOS [244]. In the TME, cancer cells undergo aerobic glycolysis, consume large amounts of glucose, produce lactate and H^+, and release elevated CSF1, promoting the polarization of M1 macrophages to immunosuppressive M2 macrophages [245]. M2 macrophages, activated by elevated IL-4 and IL-10, exhibit increased OXPHOS and fatty acid oxidation (FAO) by which lipoproteins generate abundant acetyl-CoA to fuel the TCA cycle [245].

The M2 phenotype of macrophages may be sustained by lipid catabolism via mitochondrial FAO [246]. Inhibition of long-chain FAO enzyme carnitine palmitoyltransferase I (CPT-1) can impair the M2 polarization [247]. Thus, FAO is regarded as a direct target for anticancer therapy as it triggers immunosuppressive signaling of tumor-infiltrating myeloid-derived cells [247]. Recent reports have provided evidence for the infiltration of lipid droplet-rich macrophages in tumors, including melanoma, colon, gastric, and prostate cancer [247, 248]. Infiltrating macrophages in colon cancer utilize unsaturated fatty acids from the TME to increase their lipid content, thereby shifting to OXPHOS-driven metabolism, which induces an anti-inflammatory phenotype in macrophages with upregulated expression of CD206 and arginase [246]. In addition, glutamine metabolism provides synergistic support for macrophage activation and induction of anti-inflammatory immune responses [249]. The production of α-ketoglutarate via glutaminolysis promotes differentiation and metabolic reprogramming of anti-inflammatory macrophages via Jumonji domain containing-3 (Jmjd3)-dependent epigenetic modifications [249]. M2 macrophages' specific metabolic features can directly and negatively affect effector T cell function within tumors through ARG1 [242, 250]. The overexpression of ARG1 drives the production of tumorigenic polyamines or IDO1 (an enzyme that degrades tryptophan in the TME) and produces immunomodulatory kynurenine. These substances are upregulated in the TME and promote tumor proliferation and progression [251]. Thus, TAMs and their impact on the overall metabolic profile of the TME have a significant influence on tumor progression, which are expected to be promising targets for the development of novel anticancer agents.

5.3 Mitochondrial regulation of CAFs

CAFs are an important non-malignant cell population in solid tumors and have a significant impact on shaping the TME and promoting tumor metastasis [252]. CAFs form a network of metabolic interactions with tumor cells through mitochondrial metabolic activities [253]. Glycolytic CAFs secrete lactate and pyruvate to fuel the TCA cycle of malignant cells and support mitochondrial metabolism [254, 255]. Tumor cells use CAF-derived lactate to increase the NAD^+/NADH ratio and also enhance mitochondrial biosynthesis via the SIRT1-PGC-1α pathway, promoting cancer aggressiveness [161]. In addition, malignant cells use CAF-secreted alanine and glutamine to support mitochondrial metabolism, and CAF-derived glutamine maintains glutamine-addicted ovarian tumor cell proliferation [256–258]. Lactate from cancer cells also serves as a fuel source for CAFs, further enhancing its tumor-promoting activity [259].

The tumor-specific metabolic profile of CAFs indirectly influences tumor progression by directing T cell differentiation and function to promote immunosuppression in TME. Glycolytic CAF-secreted lactate directly overcomes immunosurveillance by reducing CD4$^+$ Th1 populations resulting from T-bet degradation and by promoting FoxP3-mediated conversion of Naïve T cells to regulatory T cells (Tregs) [260, 261]. Lactate uptake by Tregs also supplies the TCA cycle and promotes phosphoenolpyruvate synthesis, thereby maintaining their inhibitory properties and supporting proliferation [262]. Lastly, glucose consumption by both tumor cells and CAFs reduces glucose abundance in the TME, which negatively affects the tumor-specific killing of highly glycolytic effector T cells [263]. Taken together, mitochondria are not only a key platform for CAFs' metabolism but also a core factor in their interaction with tumor cells and immune cells to co-shape a microenvironment conducive to tumor metastasis [252].

6 Advances and applications of mitochondria-targeted therapies

Due to the need for ATP to support growth, the mitochondrial structure and function in cancer cells differ from those in normal cells [264]. Compared with normal cells, tumor cells exhibit complex metabolic processes and increased responsiveness to mitochondrial regulation. Mitochondrial targeting drugs (MTDs) that target mitochondrial metabolism, mitochondrial dynamics, and mitochondria-mediated immunotherapy have been shown to be effective in several cancer models and therapeutic applications (Table 3).

6.1 Tumor therapies targeting mitochondrial metabolism

Tumor therapeutic approaches targeting mitochondrial metabolism have focused on exploiting the unique bioenergetic needs of tumor cells, with a particular focus on OXPHOS and the TCA cycle. Niclosamide inhibits mitochondrial OXPHOS and reduces tumor invasive and metastatic properties by targeting S100A4, a major metastasis-promoting protein, in lung and colon cancers [265]. Li et al. reported that enhanced glycolysis in HCC promotes resistance to sorafenib, and a combination of sorafenib and aspirin induced a shift in tumor metabolism toward OXPHOS, synergistically inhibiting tumor progression [266]. Researchers aim to induce high levels of ROS and thus lead to apoptosis of tumor cells by using ETC inhibitors such as metformin [267], tamoxifen derivatives [268], or MitoVES [269] (a mitochondrially targeted analog of vitamin E succinate). These compounds specifically target complexes in the ETC, such as complex I and complex II, to inhibit ATP synthesis, which in turn impairs tumor growth. In addition, natural products such as baicalin [270], amooranin [271], and trachelosides [272] also exhibit antitumor effects via mitochondria-mediated apoptotic mechanisms, which are manifested by a decrease in MMP and an increase in ROS.

In addition to OXPHOS, therapeutic strategies have also been developed targeting the TCA cycle and glutamine metabolism. Mutations in enzymes like isocitrate dehydrogenase (IDH1 and IDH2) [273, 285] and succinate dehydrogenase (SDH) [286] can drive cancer progression, making them preferred therapeutic targets. Therapeutic agents inhibiting mutant IDH1 and IDH2 have been tested in clinical trials in acute myelogenous leukemia (AML) and solid tumors,

Table 3 Summary of MTDS in different cancers

Drug name	Mechanism	Targeted cancer types	**Ref**
Niclosamide	Inhibited mitochondrial OXPHOS and reduced tumor invasive and metastatic properties by targeting S100A4	Lung and colon cancers	[265]
Sorafenib + aspirin	Shifted tumor metabolism from glycolysis to OXPHOS	HCC	[266]
Metformin	Inhibited complex I-mediated mitochondrial respiration and TCA cycle functions	Breast cancer	[267]
MitoTam	Inhibited complex I-driven respiration, leading to elevated ROS production and cell death	Breast cancer	[268]
MitoVES	Induced high levels of ROS and apoptosis by targeting complex II	Breast and colon cancer	[269]
Baicalin	Induced apoptosis through decreasing MMP and increasing ROS	Colorectal cancer	[270]
Amooranin			[271]
Tracheloside			[272]
IDH1/IDH2 inhibitors	Inhibited IDH1 and IDH2 in the TCA cycle	AML, solid tumors	[273, 274]
CPI-613	Inhibited α-KGDH and PDH in the TCA cycle	AML, pancreatic cancer	[275, 276]
CB-839	Targeted glutamine metabolism	NSCLC	[277]
Mdivi-1	Enhances cisplatin-induced apoptosis; inhibited mitochondrial recruitment to the lamellipodia	Cholangiocarcinoma, breast cancer	[140, 278]
Leflunomide	Reduced mitochondrial mass and OXPHOS by promoting Mfn2 expression and enhancing mitophagy	Pancreatic cancer	[279]
MYLS22	Enhanced NF-κB signaling pathway activity and angiogenesis gene expression in endothelial cells	Melanoma	[127]
IR-780	Induced ICD by destroying cancer cells to fully expose TAAs	Solid tumor	[280]
MRT	Released DAMPs caused by heat stress–damaged mitochondria, resulting in the reactivated immunoresponse of macrophages	HCC	[281]
OPDEA-PDCA	Inhibited PDHK1 to trigger mitochondrial oxidative stress and ICD	Osteosarcoma	[282]
Linoleic acid	Improves CTL function and promotes memory T cell differentiation	Multiple myeloma, lymphoma, melanoma and neuroblastoma	[283]
MPC inhibitors	Promotes differentiation of T cells toward a memory phenotype	Leukemia	[284]

suggesting a manageable safety profile as well as clinical benefit [273, 274]. CPI-613, a lipoic acid analog that inhibits the key enzyme complexes α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (PDH) in the TCA cycle, has shown potential in treating pancreatic cancer and AML in early clinical trials [275, 276]. Furthermore, given that glutamine is used as fuel in many different types of cancers to provide nutrients and biosynthetic precursors for their growth [90, 287, 288], inhibition of glutamine metabolism by targeting glutaminase (GLS) has emerged as a promising strategy [289–291]. GLS inhibitors such as CB-839 have shown potent antitumor effects in a variety of cancers, including those resistant to chemotherapy. GLS inhibitors combined with erlotinib were demonstrated to downregulate glutamine and glycolytic metabolism in NSCLC, thereby limiting tumor proliferation and progression [277]. In the coming years, the rational combinations of mitochondrial inhibitors with standard of care treatment including chemotherapy or radiotherapy are expected to develop novel and efficacious anticancer treatments.

6.2 Tumor therapies targeting mitochondrial dynamics

Tumor therapies targeting mitochondrial dynamics take advantage of the imbalance between mitochondrial fission and fusion in cancer cells, which is tightly linked to tumor growth, invasion, and metabolic reprogramming. Mdivi-1, a selective DRP1 inhibitor that prevents mitochondrial fission and promotes the formation of extended mitochondrial networks, exhibits therapeutic potential in a variety of malignant diseases [292]. In neurons, Mdivi-1 protects cells from excitotoxicity [293], whereas in cholangiocarcinoma, it enhances cisplatin-induced apoptosis [278] and inhibits oxidative metabolism and tumor cell proliferation [294]. Besides, Mdivi-1 was also reported to induce apoptosis and inhibit the growth of brain tumor [295]. In breast cancer, mitochondrial elongation or clustering caused by DRP1 silencing or Mfn1 overexpression was shown to inhibit mitochondrial recruitment to the lamellipodia, which attenuated cell migration and reduced the metastatic potential of breast cancer [140].

In addition to the inhibition of mitochondrial fission, there is also promising evidence that targeted modulation of mitochondrial fusion may be a feasible approach for the treatment of tumor metastasis. In pancreatic cancer, oral leflunomide promotes upregulation of Mfn2 expression in tumors, and an Mfn2-mediated increase in mitochondrial fusion enhanced mitophagy, which proportionally reduced mitochondrial mass and OXPHOS, exerting an inhibitory effect on tumor growth [279]. In addition, Mfn2 was also reported to inhibit tumor progression by regulating epithelial-mesenchymal transition in thyroid cancer [296]. Recent evidence suggests that MYLS22, a small molecule compound that specifically inhibits OPA1, is effective in suppressing melanoma growth and metastasis [127]. In addition to promoting mitochondrial elongation, OPA1 also enhances NF-κB signaling pathway activity and angiogenesis gene expression in endothelial cells [127], revealing therapeutic target potential for tumors that are resistant to vascular endothelial growth factor receptor (VEGFR) inhibitors. Significant progress has been made in understanding the role of mitochondrial dynamics in cancer therapies, and exploration of the exciting new area holds promise for the development of novel targeted therapies against metastatic disease.

6.3 Mitochondria-targeted tumor immunotherapy

Immunotherapy has emerged as the most promising cancer treatment strategy due to its powerful role in enhancing the specificity of immune responses and its greater efficacy in reducing tumor metastasis and recurrence compared with traditional therapies [297–299]. In recent years, immunogenic cell death (ICD), which can convert dying cancer cells into therapeutic vaccines and stimulate systemic antigen-specific antitumor immune responses, has been studied extensively in the field of cancer immunotherapy [300]. However, the application of conventional ICD inducers in anticancer immunotherapy is limited by the lack of tumor-targeting and accumulation as well as low levels of ICD induction [301]. Therefore, many studies are currently focusing on mitochondria in cancer cells, which are organelles that play a key role in the immune system and are important targets for developing effective ICD inducers for cancer immunotherapy [302, 303].

Many new nanostructured molecules and therapeutic strategies focusing on the enhancement of mitochondria-mediated ICD have been developed [304]. IR-780, a mitochondrial-targeted small molecule, was shown to induce ICD by destroying cancer cells to fully expose tumor-associated antigens (TAAs), thereby effectively inhibiting tumor growth and metastasis [280]. A recent study on HCC demonstrated that nanomedicine MRT could effectively activate TAMs and inhibit distal tumor growth by causing ICD in tumor cells and releasing DAMPs including ATP and HSP 70 via magnetic heat therapy (MHT) [281]. Another study has designed a mitochondria-homing polymer micelle system, called OPDEA-PDCA, which exerted anticancer effects by inhibiting pyruvate dehydrogenase kinase 1 (PDHK1) and then triggering mitochondrial oxidative stress within tumor cells, thereby inducing ICD [282]. The combined therapy of OPDEA-PDCA and anti-PD-L1 monoclonal antibody in that study exerted a significant effect on prolonging the survival of activated T cells and inhibiting osteosarcoma progression. Overall, further studies are still needed to investigate how to minimize off-target effects and systemic toxicity, enhance

the stability and controlled release of the therapeutic payload in the TME, and take into account the immunological properties of the nanocarriers themselves to enhance the overall ICD efficacy, thus paving the way for a more effective and personalized cancer therapy.

Adoptive T cell therapy (ACT), a revolutionary cancer immunotherapy strategy, with either allogeneic or autologous immune cells, has shown unequivocal therapeutic benefits in a significant proportion of cancer patients [305, 306]. The adoptive transfer of tumor-specific T cells results in durable and complete disease regression in some patients with metastatic cancer [307, 308]. However, short persistence and early exhaustion of T cells are still major limitations to the efficacy and broad application of immunotherapy [309]. Among cell exhaustion characteristics, impaired mitochondrial function and dynamics are considered hallmarks [236]. Therefore, how to collect T cells with mitochondria that are in a good functional state and can be maintained for a long time is a current research concern.

Numerous studies have reported various ways to harvest sufficient long-lived effective T cells and improve the antitumor responses of ACT. Sukumar et al. described a simple and clinically feasible method to isolate and segregate functionally robust T cells based on a single metabolic parameter: MMP [310]. Low-MMP $CD8^+$ T cells display the metabolic profile of long-lived T cells (reduced glycolysis and increased mitochondrial spare respiratory capacity), thus exhibiting enhanced *in vivo* persistence, augmented autoimmunity, and greater antitumor capacity. Nava-Lauson et al. demonstrated that linoleic acid, a major positive regulator of cytotoxic T lymphocyte (CTL) activity, enhances the formation of ER-mitochondria contacts [283]. This enhancement promotes calcium signaling and mitochondrial energetics, which in turn prevent CTL exhaustion and enhance antitumor responses. Linoleic acid is able to ameliorate ACT efficacy and to broaden its application for the treatment of a wide range of malignancies. In CAR-T cell manufacturing, memory T cells exhibit superior and durable antitumor activity due to their longevity and self-renewal properties [311, 312]. Wenes et al. have demonstrated that short-term inhibition of the mitochondrial pyruvate carrier in activated T cells promotes memory differentiation and enhances antitumor activity upon ACT by facilitating acetyl-CoA production via glutamine metabolism and FAO, resulting in enhanced histone acetylation and increased chromatin accessibility on pro-memory genes [284]. There have been many studies that have achieved remarkable results or made significant progress. However, the mechanisms by which mitochondrial metabolism affects CAR-T cell survival, function, and differentiation remain unclear and await further excavation.

6.4 Clinical significance and prospects of mitochondrial-targeted therapy

Given the crucial role in tumor cell immune escape, tumor progression, and treatment resistance, mitochondria may be the Achilles' heel of cancer treatment [21]. Traditional strategies that target mitochondria usually induce changes in cellular energy metabolism or directly affect the function of mitochondrial antiapoptotic proteins [21, 313]. In future studies, it would be ideal to abrogate mitochondrial dysfunction and energy imbalance of immune cells while inhibiting tumor cell metabolism, ultimately improving the clinical prognosis of patients [21, 59].

Recent publications have revealed the superior tumor therapeutic effects of a group of triphenylphosphonium-modified molecules (e.g., Mito-honokiol, Mito-magnolol, Mito-metformin, Mito-atovaquone, Mito-hydroxyurea) [314]. These modified molecules accumulate more efficiently in tumor cell mitochondria and inhibit mitochondrial respiration, induce ROS, and activate AMPK and redox transcription factors, thereby inhibiting cancer cell proliferation. In addition, MTD treatment inhibits tumor suppressor immune cells, including myeloid-derived suppressor cells and Tregs, and enhances antitumor immune effects. For example, metformin can effectively inhibit mitochondrial complex I and stimulate superoxide, which in turn inhibits tumor cell proliferation [315]. AMPK is a major regulator of cellular energetic homeostasis and is usually activated by increased intracellular AMP. Mito-metformin, an OXPHOS inhibitor, was found to inhibit the proliferation of immunosuppressive cells in TME and enhance antitumor immunity by activating AMPK phosphorylation, which in turn inhibits STAT3 signaling in cancer cells [314–316]. More researches are needed to develop precise and personalized anticancer therapies and to evaluate the efficacy and safety of this approach in clinical applications.

7 Conclusion and perspective

Mitochondria participate in the activation and regulation of various signaling pathways that mediate functional changes related to cell metabolism and immunity through mitophagy, mitochondrial transfer, and genetic alterations. Cancer cells adapt to the harsh conditions of the TME by regulating mitochondrial activity and even promote tumor invasion and metastasis by influencing surrounding stromal cells or circulating immune cells through mitochondria-related manners. The mitochondrial mechanisms underlying metastasis remain incompletely elucidated, and there are key obstacles that require thorough investigation to overcome. Delving into these details is vital for improving our comprehension of the fundamental processes governing metastatic progression and fostering the development of innovative therapeutic strategies.

Author contribution F.C., J.G. and S.W. drafted and conceived the initial manuscript. Y.X., W.Z., H.Z., Z.Z., T.C., and E.Y. provided the essential ideas of this work. F.C, Y.X., W.Z., H.Z., T.C., E.Y., and H.L. drew the figures and arranged the tables. Z.Y., J.G., and S.W. revised the manuscript.

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Declarations

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