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Review Article

The role of mitochondrial dynamics in human cancers

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Abstract: Mitochondria are crucial cellular organelles. Under extracellular stimulations, mitochondria undergo constant fusion and fission dynamics to meet different cellular demands. Mitochondrial dynamics is regulated by specialized proteins and lipids. Dysregulated mitochondrial dynamics has been linked to the initiation and progression of diverse human cancers, affecting aspects such as cancer metastasis, drug resistance and cancer stem cell survival, suggesting that targeting mitochondrial dynamics is a potential therapeutic strategy. In the present review, we summarize the molecular mechanisms underlying fusion and fission dynamics and discuss the effects of mitochondrial dynamics on the development of human cancers.

Keywords: Mitochondrial dynamics, human cancers, lipids, cancer stem cells

Introduction

Mitochondria are semiautonomous intracellular organelles vital to cellular physiological activity. As the main site of oxidative respiration to produce ATP, mitochondria are not only the cellular 'powerhouse' but also the site where many crucial metabolic processes take place [1]. Because of their functional diversity, mitochondria play important roles in cell proliferation, apoptosis, calcium ion storage and reactive oxygen species (ROS) generation [2, 3]. Furthermore, mitochondria play an important role in immunity and inflammation [4].

In most cells, mitochondria are highly dynamic and, through fusion and fission, undergo constant changes in number and morphology in response to metabolic and extracellular insults [5]. These fission and fusion events determine the shape of mitochondria and further influence their function.

Mitochondrial dynamics contributes to the genesis and progression of various kinds of human cancers [6]. Elucidating the role of mitochondrial dynamics in human cancers is of great importance, as this understanding will offer new insights into related treatments.

After presenting a detailed description of protein mediators and lipids that have been acknowledged to regulate mitochondrial fusion and fission, this review focuses on summarizing fundamental cellular functions impacted by unbalanced fusion and fission. In addition, an overview of cancers involving dysregulated mitochondrial dynamics is presented in the third section.

Regulation of mitochondrial fusion and fission

Mitochondrial dynamics is exquisitely regulated by proteins and lipids (**Figure 1**).

Proteins involved in mitochondrial fusion

In mammalian cells, the fusion machinery includes three essential GTPases, mitofusin (Mfn) 1 and 2 on the outer mitochondrial membrane (OMM) and optic atrophy protein 1 (Opa1) on the inner mitochondrial membrane (IMM) [7, 8].

Mfn1 and Mfn2 coordinate OMM fusion. The c-terminal heptad repeats of Mfn1 and Mfn2 have been shown to form an intermolecular antiparallel coiled coil via which adjacent mitochondria may be drawn together and initiate mixing of their lipid bilayers, leading to fusion of the OMM [9].

Opa1 drives IMM fusion [10]. Opa1 is localized to the mitochondrial intermembrane space and

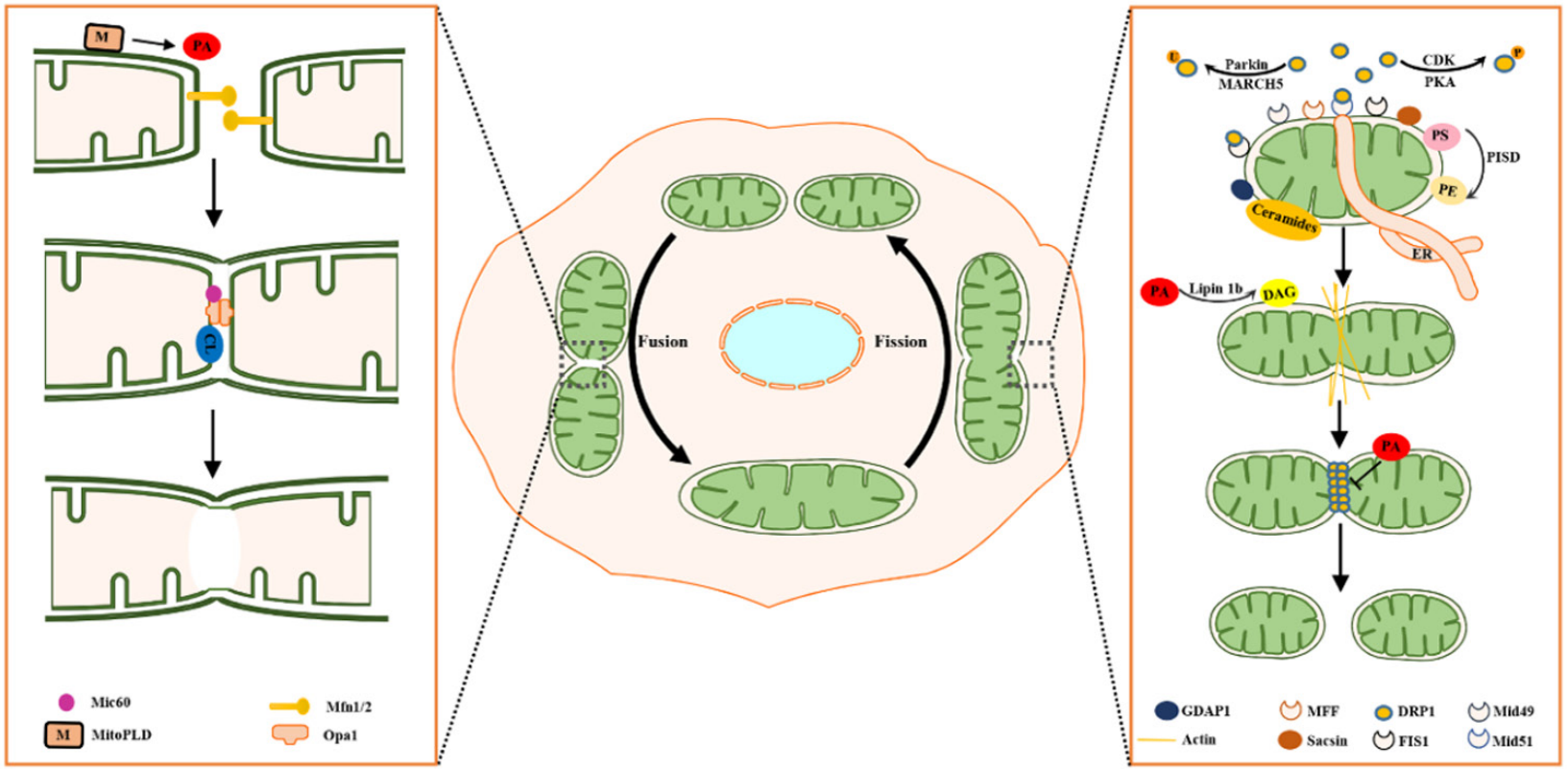

Figure 1. A schematic diagram of mitochondrial dynamics. Human mitochondria undergo constant fusion and fission dynamics. The fusion of the OMM is mediated by Mfn1/2. PA generated by MitoPLD promotes fusion of the OMM. CL and Opa1 coordinate IMM fusion. Mic60 also interacts with Opa1. ER tubules mark sites of fission. During mitochondrial fission, Drp1 is recruited to mitochondria by receptors such as Fis1, Mid49, Mid51 and Mff. GDAP1 and sacsin are two additional proteins localized in the OMM that facilitate fission. Drp1 activity is regulated by posttranslational modifications such as phosphorylation and ubiquitination. The preconstriction process is completed by actin filaments, and Drp1 performs mitochondrial scission. Lipids, including ceramides, PA and DAG, participate in mitochondrial fission. PA, phosphatidic acid; OMM, outer mitochondrial membrane; CL, cardiolipin; Drp1, dynamin-related protein 1; DAG, diacylglycerol; ER, endoplasmic reticulum.

the IMM. OPa1 has 8 isoforms, and the steady-state morphology of mitochondria depends on the balance of the long and short Opa1 isoforms [11]. Opa1 is likely to interact with Mfns to form intermembrane protein complexes that couple OMM fusion to IMM fusion [12].

The mitochondrial structural protein Mic60, also called mitofilin, appears to be a key player in regulating mitochondrial shape [13]. Increased levels of Mic60 suppress mitochondrial fission in neurites, producing elongated neuritic mitochondria [14]. Mic60 also interacts with Opa1 [15]. MitoPLD belongs to the phospholipase D superfamily of signaling enzymes that generate phosphatidic acid (PA). MitoPLD is anchored to the mitochondrial surface [16], and MitoPLD-generated PA facilitates mitochondrial fusion [17].

Mitochondrial fission proteins

Endoplasmic reticulum (ER) tubules contact mitochondria and mark the sites of mitochondrial division [18]. Several outer membrane proteins, including Mff, Fis1, Mid49 and Mid51, have been identified as dynamin-related protein 1 (Drp1) receptors [19-21]. Drp1 is recruited to the mitochondrial surface via its transmembrane receptors and assembles into oligomeric complexes. Before the scission of mitochondria by Drp1, preconstriction is completed by actin and nonmuscle myosin II. A study reported that myosin II induced stochastic deformations of the interstitial actin network and exerted pressure on the mitochondrial surface, promoting mitochondrial fission [22].

The activity of Drp1 is regulated by posttranslational modifications. Several different posttranslational modifications of Drp1, including phosphorylation, ubiquitination and sumoylation, regulate its activity, thus influencing the fission process [23-26].

Moreover, human Fis1 was reported to regulate mitochondrial fission in the absence of Drp1. Fis1 binds to Mfn1, Mfn2 and Opa1, thus inhibiting their GTPase activity and the fusion machinery [27].

GDAP1 is another protein involved in mitochondrial fission events. This protein is localized in the OMM [28]. In animal models, neurons from GDAP1-knockout mice show large and defective mitochondria [29].

Sacsin localizes to the OMM in a variety of cell lines [30]. Loss of sacsin induces the generation of hyperfused mitochondria. The results of a coimmunoprecipitation assay showed that sacsin interacts directly with Drp1 [31].

Syntaphilin (SNPH) has been identified to inhibit mitochondrial trafficking in neurons [32]. SNPH can be ubiquitinated at Lys111 and Lys153 in the microtubule-binding domain by the E3 ligase CHIP. SNPH ubiquitination results in anchoring of SNPH to tubulin, which inhibits the movement of mitochondria. Perturbation of SNPH ubiquitination causes recruitment of Drp1 to mitochondria [33].

Lipids involved in regulating mitochondrial dynamics

Apart from proteins, accumulating evidence implies the striking role of lipids in the governance of mitochondrial dynamics.

Phospholipids are the primary lipid components of the mitochondrial membrane. Cardiolipin (CL) is a mitochondria-specific phospholipid [34]. It is synthesized from PA in the IMM [35]. CL is related to the assembly of Opa1. Liposomes containing CL bind to purified Opa1 and Mgm1, stimulating their assembly into liposomes [36]. In addition, CL has been shown to stimulate the oligomerization of Drp1, which induces its tubulation and sequential mitochondrial fission [37, 38].

PA is produced mainly in the ER and is then transported to the OMM through an ER-mitochondria contact site [39]. PA promotes mitochondrial fusion possibly by creating a negative curvature in the opposing OMM [40]. PA also regulates mitochondrial fission by interacting with Drp1. After its oligomerization on mitochondria, Drp1 is blocked by PA and the saturated acyl chains of phospholipids, which makes mitochondria resistant to the division induced by mitochondrial stress [41, 42].

Phosphatidylethanolamine (PE) and phosphatidylserine (PS) are two other mitochondrial membrane components. PS is well known for its role in apoptosis. PE is produced from PS by phosphatidylserine decarboxylase (PISD) [43]. A novel tumor suppressor, LACTB, reduces the levels of mitochondrial PISD possibly through its proteolytic activity, thus altering the generation of PE. A reduction in the PE/PS ratio shifts

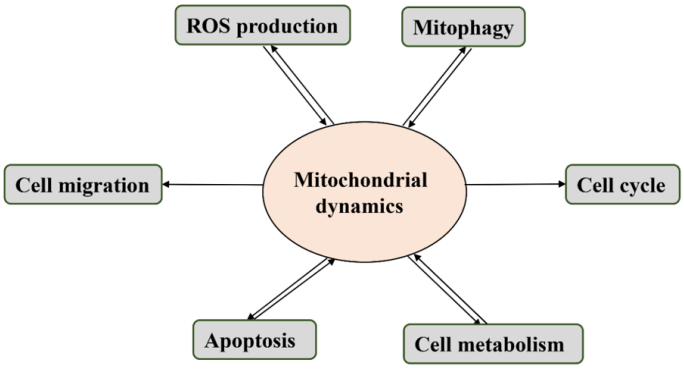

Figure 2. Cellular physiological activities affected by mitochondrial dynamics. Mitochondrial dynamics is tightly linked to the cell cycle, apoptosis, cell migration, mitophagy, apoptosis and ROS production.

mitochondrial dynamics toward fission and exerts an anticancer effect [44].

Diacylglycerol (DAG) triggers mitochondrial fission [45]. DAG may drive actin filament polymerization by activating RhoA at the sites of ER constriction, which could shrink mitochondria to an appropriate diameter for Drp1 to encircle and cleave [46, 47].

Ceramides are synthesized in both the OMM and IMM [48]. Ceramides stimulate mitochondrial fission in cardiomyocytes [49]. Human choriocarcinoma cells treated with ceramides 16:0 exhibited mitochondrial fragmentation through increases in the p-Drp1/Drp1 ratio and Mfn2 expression [50].

Biological functions of mitochondrial dynamics

The continuous fusion and division processes of mitochondria are crucial for essential physiological functions of cells (**Figure 2**). The main cellular functions involved in the link between mitochondrial dynamics and cancer development are summarized herein.

Mitochondrial dynamics and ROS production

ROS, short-lived molecules consisting of unpaired electrons, are considered byproducts of cellular metabolism. The mitochondrial electron transport chain is a major contributor to ROS production in cancer cells [51]. Accumulating evidence demonstrates that mitochondrial morphology and ROS levels are closely related. For example, parallel changes in mitochondrial morphology and ROS levels were found in patient primary fibroblasts [52]. Besides, genetic ablation of Mfn1 or Mfn2 led to elevated ROS levels, and mitochondrial fission promoted ROS production [53, 54]. In turn, experimental results revealed that overproduced mitochondrial ROS altered posttranslational modifications of Drp1 and affected other mediators, such as Opa1 and Mfns, causing mitochondrial dysfunction [55-57].

ROS homeostasis is required for cell survival. Due to metabolic activity, gene mutation and hypoxia, cancer cells yield high levels of ROS. Depending on enhanced antioxidant activity, cancer cells managed to maintain moderate levels of ROS, which facilitate tumor initiation and progression. ROS participate in various cell signaling pathways, such as the Ras/MAPK/ERK, PI3K/Akt and NF-κB pathways [58]. These pathways have been linked to cellular transformation, cancer cell proliferation, apoptosis resistance, cancer stem cells (CSCs) maintenance and cancer metastasis [59].

In general, aberrant mitochondrial dynamics might enhance ROS production, and high concentrations of ROS can modify fusion and fission effectors, forming a feedback loop.

Cell migration

Metastasis accounts for most cases of cancer progression, resulting in failure of clinal therapy and death of the patients. Cancer cells enter blood or lymphatic vessels through intravasation. After extravasation from these vessels, they form cloning lesions in distant organs [60]. Cell migration is a crucial step in metastasis. Accumulating data suggest the role of mitochondria in the dissemination of cancer cells. For example, mitochondrial dynamics regulates the migration and invasion of breast cancer cells; researchers found higher expression of Drp1 and lower expression of Mfn1 in metastatic breast cancer cells than in their nonmetastatic counterparts [61]. Recently, additional evidence indicating the regulatory role of mitochondrial dynamics in cancer metastasis has emerged [33, 62-64].

Mitochondrial fusion and fission influence mitochondrial transportation in lymphocytes as well as in cancer cells. Mitochondria are redistributed during lymphocyte migration. Experimental results show that mitochondria accumulate at the uropod of polarized lymphocytes in a manner dependent on unperturbed mitochondrial fission. Moreover, dysregulation of mitochondrial fusion/fission suppresses lymphocyte polarization and migration [65].

Researchers have investigated the connection between mitochondrial dynamics and T cell metabolism. In contrast to memory T cells, activated effector T cells maintain a fused mitochondrial network. Memory T cells require mitochondrial fusion for development and survival, and forced fusion promotes the generation of memory-like T cells regardless of the presence of activating signals [66]. In animal models, T cell mitochondrial fusion was shown to enhance antitumor immune responses [67].

Mitophagy

mtDNA is frequently exposed to ROS and liable to mutate and damage. Accumulation of mtDNA mutations gradually leads to functional impairment of respiratory chain complexes and finally reduces the bioenergetic capacity. Damaged mitochondria are degraded through a specialized form of macroautophagy called mitophagy [68]. The molecular pathway of mitophagy is divided into two pathways according to differential dependency on Parkin: the phosphatase and tensin homologue (PTEN)-induced putative kinase 1 (PINK1)-Parkin pathway and the Parkin-independent pathway.

Mitochondrial dynamics has been found to be intertwined with mitophagy. Mitochondrial fission plays an important role, as mitophagy is preceded by mitochondrial division, after which fragmented mitochondria are encapsulated by autophagosomes [69]. Accordingly, overexpression of Fis1 triggers mitophagy, and depletion of Fis1 or overexpression of the dominant-negative Drp1 K38A mutant attenuates mitophagy [70].

Researchers found that the mammalian mitophagy receptor FUNDC1 interacts with and recruits LC3 to mitochondria for mitophagy. FUNDC1 interacts with both DNM1L/Drp1 and Opa1 to coordinate mitochondrial dynamics and mitophagy [71]. Another study revealed that PINK1 impairs the anti-fission machinery to ensure segregation of damaged mitochondria. PINK1 indirectly interacts with Drp1 and enhances Drp1 activity [72]. In addition, the SNARE protein Syntaxin 17 (STX17) was recently identified to interact with Fis1. Fis1 loss triggers abnormal STX17 accumulation on mitochondria, which promotes self-oligomerization of STX17 and mitophagy [73].

Mitochondrial dynamics and cell metabolism

A major characteristic of cancer cells is their reduction in mitochondrial respiration and their predilection to use glycolysis to obtain energy even under aerobic conditions [74]. However, many types of cancer cells obtain energy via oxidative phosphorylation [75]. Metabolic reprogramming of cancer cells has been identified to occur during tumorigenesis and highlights the role of mitochondria during oncogenesis. Cellular metabolic changes impact mitochondrial dynamics, and mitochondrial dynamics in turn alter the state of cell metabolism.

Mitochondrial dynamics has been linked to the balance between energy demand and nutrient supply. Fusion is positively associated with increased ATP production, while inhibition of fusion results in oxidative phosphorylation impairment, mtDNA depletion, and ROS production [76]. In skeletal muscle, the liver and the pancreas, manipulation of key fusion and fission proteins causes metabolic variations [77]. Similarly, in cancer cells, mitochondrial dynamics plays a pivotal role in metabolic reprogramming. In prostate cancer cells, Drp1 upregulation is required for metabolic reprogramming because it controls the mitochondrial pyruvate transport complex [78]. Furthermore, Mfn1 regulates metastasis in hepatocellular carcinoma (HCC) by shifting cell metabolism from glycolysis to oxidative phosphorylation [79]. Similar experimental results have also been reported in other human cancers [64, 80-82].

On the other hand, metabolic changes influence the amount and activity of mitochondria-shaping mediators. For example, serine deprivation affects mitochondrial function and inhibits colorectal cancer cell proliferation through ceramide metabolism. Supplementation of C 16:0-ceramide was shown to partially restore

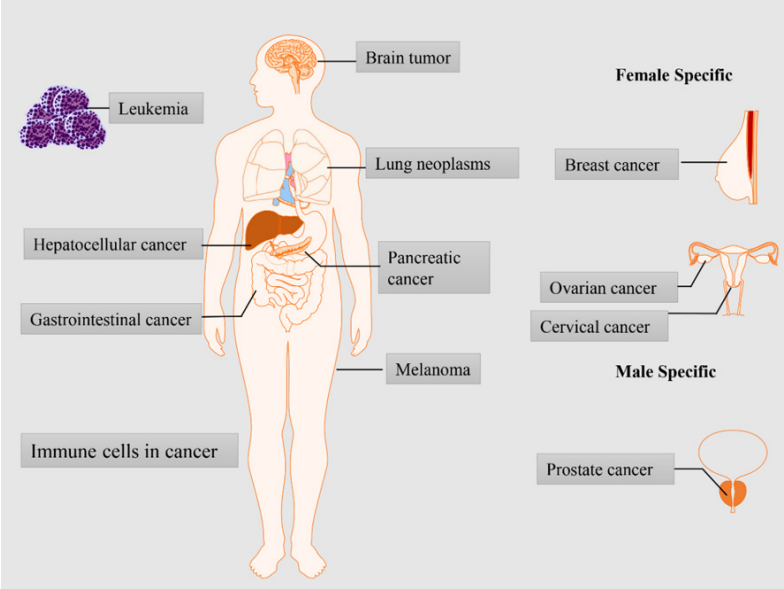

Figure 3. Human cancers connected with dysregulation of mitochondrial dynamics.

mitochondrial fragmentation [83]. Another study reported that glucose starvation causes KAP1 phosphorylation on Ser473, which limits mitochondrial hyperfusion through a reduction in the Mfn2 level and favors breast cancer cell survival [84]. Similar types of interplay has been studied in several kinds of immune cells [85].

Apoptosis

Mitochondria play a critical role in cell apoptosis. An important step during apoptosis is mitochondrial outer membrane permeabilization (MOMP), which releases cytochrome c and other proapoptotic factors from the intermembrane space into the cytosol [86]. MOMP is mediated by translocation of cytosolic BAX and BAK to mitochondria, where a pore is formed in the OMM, allowing the release of proapoptotic proteins.

Multiple lines of evidence show that Drp1 is crucial in cell apoptosis. Drp1 activity is required for cytochrome c release and subsequent apoptotic events. For instance, SUMOylation of Drp1 stabilizes ER/mitochondrial contact sites that are important for remodeling of cristae and release of cytochrome c [87]. Mitochondrial fission appears to be an upstream event of apoptosis [88]. However, increased mitochondrial fission does not necessarily correlate with apoptosis activation [89]. Mfn1 and Mfn2 also control cell apoptosis by interacting with Bak or by triggering an influx of Ca^{2+} into mitochondria [90, 91].

Opa1 protects cells from apoptosis by preventing cytochrome c release. Opa1 sustains the tightness of cristae junctions, a feature that likely regulates the mobilization of cytochrome c [92]. Similarly, another report found that Opa1 blunts cytochrome c release in hepatocellular cells [93].

In addition, Bax and Bak have been reported to regulate mitochondrial dynamics in healthy cells. Bax can induce mitochondrial fusion by promoting the assembly of Mfn2 [94].

Mitochondrial dynamics in the cell cycle

Mitochondrial dynamics is critical during cell cycle regulation. In G1 and G2 phases, mitochondria form an interconnected network [95, 96]. However, mitochondria become fragmented during S phase and mitosis [97]. Mediators of mitochondrial dynamics, including Drp1, Fis1, Opa1 and mfn proteins, are linked to cell cycle phase transition [98-100]. For instance, inhibition of Drp1 causes cell cycle arrest in G1 phase by affecting cyclin E accumulation [101], and Mfn2 overexpression in VSMCs causes G0/G1 phase arrest [102].

The serine/threonine kinase Aurora A (AURKA) is overexpressed in several cancers [103, 104]. AURKA was reported to promote mitochondrial fission through phosphorylation of RALA in the cytosol [105]. In 2018, a study showed that at endogenous levels, AURKA induces mitochondrial fragmentation but enhances mitochondrial fusion when overexpressed [106].

Imbalanced mitochondrial dynamics in human cancers

Dysregulation of mitochondrial dynamics has been frequently reported to drive malignant

phenotypes of cancer (**Figure 3**). Various evidence implicating mitochondrial dynamics in the onset and progression of cancer has emerged (**Table 1**). We summarize the publications from the past five years below.

Hepatocellular cancer

Mitochondrial fission has been reported to promote cell migration, autophagy, tumor-associated macrophage infiltration and HCC progression [62, 107]. The Drp1/Mfn1 expression ratio was found to be increased in HCC tissues and associated with poor prognosis. Enhanced mitochondrial fission mediated by elevated ROS production was found to promote the survival of HCC cells in vitro and in vivo [108]. Depletion of Mfn1 induced epithelial-to-mesenchymal transition of HCC cells [79]. However, another study showed that mitochondrial fusion also supported liver tumor cell growth [81]. Moreover, metabolic reprogramming via mitochondrial elongation was found to be essential for hepatocellular cancer cell survival and adaptation to energy stress [80].

Ovarian cancer

Ovarian cancer is the major cause of death among gynecologic cancers [109]. Previous studies found that ovarian cancer cells exhibit increased Drp1 expression. Drp1 was shown to be coexpressed with cell cycle genes and to support the proliferation of ovarian cancer cells [110]. Similarly, a study reported that under hypoxic conditions, mitochondrial fission caused cisplatin resistance in ovarian cancer cells [111]. In addition, salt-inducible kinase 2 was shown to enhance the Warburg effect in ovarian cancer cells through drp1-mediated fission [64].

Breast cancer

MYC was found to indirectly inhibit YAP/TAZ coactivators in breast cancer cells, thus suppressing cancer development. PLD6, an OMM-localized phospholipase, was identified as the mediator of MYC activity via enhancement of mitochondrial fusion [112]. In contrast, mitochondrial fission facilitates the survival, apoptosis and drug resistance of breast cancer cells [84, 113, 114]. The autophagy inhibitor liensinine was found to markedly increase apoptosis in breast cancer cells in combination with classical chemotherapeutic drugs by triggering DNM1L-mediated mitochondrial fission [115]. Moreover, novel Drp1 inhibitors, Drpitor1 and Drpitor1a, were identified to have antineoplastic potency in breast cancer cells [116].

Pancreatic cancer

The Ras oncogene is frequently mutated in pancreatic ductal adenocarcinomas, and its mutation is an early event in pancreatic tumorigenesis [117]. Expression of oncogenic Ras or MAPK pathway activation leads to increased mitochondrial fragmentation, but blocking mitochondrial fission through knockdown of Drp1 inhibits tumor growth via Erk2-mediated phosphorylation of Drp1 on Ser616 [23]. In addition, FAM49B was found to be a tumor suppressor in pancreatic ductal adenocarcinomas. FAM49B knockdown induced Drp1 phosphorylation and favored fission in cancer cells [118]. However, mitochondrial fission induced by knockdown of myoferlin was reported to inhibit cancer cell proliferation and ATP production [119].

Lung neoplasms

In non-small cell lung cancer (NSCLC), SIRT4 inhibited cancer progression by decreasing mitochondrial fission [120]. Downregulation of the oncoprotein AIM2 enhanced mitochondrial fusion [121]. Inhibition of PIM caused mitochondrial fragmentation and sensitized NSCLC cells to chemotherapy [122]. Another study showed that a fraction of endogenous MDM2 was actively imported into mitochondria and affected mitochondrial dynamics independent of p53 in lung neoplasms. MDM2 depletion resulted in enhanced phosphorylation of DRP1 on Ser637, leading to increased mitochondrial fission. Increased mitochondrial MDM2 levels strengthened the migratory and invasive properties of cancer cells [123].

Brain tumor

The identification of brain tumor initiating cells (BTICs) provided insights into human brain tumor pathogenesis. Drp1 showed activating phosphorylation in BTICs and inhibitory phosphorylation in bulk tumor cells. Suppression of Drp1 led to BTIC apoptosis and suppressed tumor growth. Drp1 activity regulated the downstream metabolic stress sensor AMP-activated

Table 1. A list of recent research results involving mitochondrial dynamics and cancer

Cancer type	Mitochondrial dynamics	Malignant property	Reference
HCC	Dynamin-1-like protein upregulation and Mfn1 downregulation	Enhancement of cell migration	[62]
HCC	Mfn1 downregulation	Depletion of Mfn1 modulated cancer metastasis via a metabolic shift	[79]
HCC	Increased DNM1L/MFN1 expression ratio	Cell survival	[108]
HCC	Drp1 upregulation	Infiltration of tumor-associated macrophages	[107]
HCC	Starvation-induced Drp1 Ser637 phosphorylation and suppression of its mitochondrial translocation	Metabolic reprogramming	[80]
HCC	Excessive fusion	Metabolic alteration Promotion of cell growth	[81]
Ovarian cancer	Drp1 phosphorylation on Ser616 promoted by SIK2	Support of cell growth and metastasis	[64]
Epithelial ovarian cancer	Correlation of Drp1 with cell cycle genes	Mitotic transition and chemosensitivity	[110]
Ovarian cancer	Hypoxia-induced increase in mitochondrial fission	Cisplatin resistance	[111]
Breast cancer	Enhanced fusion driven by myc	YAP/TAZ suppression	[112]
Breast cancer	Mfn2 downregulation	Cancer cell survival under metabolic stress	[84]
Breast cancer	Drp1 upregulation Mfn1 downregulation	Cancer cell survival	[113]
Breast cancer	DRP1 phosphorylation on Ser637	Tamoxifen resistance	[114]
Breast cancer	Liensinine treatment induced fission via DNM1L activation	Cellular apoptosis	[115]
Pancreatic cancer	Increased Drp1 phosphorylation	Tumor growth	[23]
Pancreatic ductal adenocarcinoma	Acquisition of a myoferlin-induced branched mitochondrial structure	Mitochondrial fission inhibited cancer cell proliferation	[119]
Pancreatic ductal adenocarcinoma	Enhanced mitochondrial fission	Cell proliferation and invasion	[118]
NSCLC	Mfn2 upregulation	Decreased ROS production	[121]
NSCLC	Inhibition of Drp1 phosphorylation by sirt4	Cell cycle arrest Repressed invasion	[120]
NSCLC	PIM1-inhibition induced Drp1 upregulation	Chemosensitivity	[122]
Lung cancer	Enhanced Drp1 phosphorylation caused by MDM2 depletion	Suppressed cell migration and invasion	[123]
Glioblastoma	Drp1 upregulation in BITCs	Tumor growth	[124]
Glioma	Promotion of Drp1-dependent fission by NF-κB-inducing kinase	Cell invasion	[63]
Cervical cancer	Mfn2 activation	-	[125]
Melanoma	Drp1 upregulation	Tumor growth	[127]
T-ALL	Drp1 phosphorylation on Ser616	Drug resistance	[130]
AML	Fission upregulation In LSCs	LSC self-renewal	[131]
Prostate cancer	Mff repression resulting from BRD4 knockdown	CSC exhaustion	[133]
Prostate cancer	Increased fission	Tumorigenesis	[132]
Gastrointestinal stromal tumor	Inhibition of mitochondrial fission mediated by knockdown of Nestin	Cell proliferation and invasion	[134]
Colorectal cancer	Drp1 phosphorylation	Chemoresistance	[135]
Colorectal cancer	Suppression of Drp1 phosphorylation	Inhibition of carcinogenesis	[136]

protein kinase (AMPK). Furthermore, Drp1 activation was found to be related to poor prognosis in glioblastoma, implying that mitochondrial dynamics is a novel therapeutic target for brain tumors [124]. In glioma, NF-κB-inducing kinase was found to promote mitochondrial fission and cell invasion. Drp1 was essential for NF-κB-inducing kinase-dependent cell invasion [63].

Cervical cancer

MFN2 and Rab, as well as Ras Interactor 1 (RIN1), were identified as new Smad2 binding partners required for mitochondrial fusion in HeLa cells. Inactive cytoplasmic Smad2 rapidly promoted mitochondrial fusion by recruiting RIN1 into a complex with MFN2. These results implied functional connections between Smad proteins and mitochondrial dysfunction [125].

Melanoma

Nutrient-sensing mechanistic/mammalian target of rapamycin complex 1 (mTORC1), which is frequently activated in cancer, controls cell growth and metabolism [126]. mTOR stimulates translation of mitochondrial fission process 1 (MTFP1), which is coupled to pro-fission phosphorylation and mitochondrial recruitment of DRP1 in melanoma cells. Potent active site mTOR inhibitors induce mitochondrial hyperfusion due to diminished translation of MTFP1. Additionally, MTFP1 was identified as a critical effector of mTORC1 to govern cell fate decisions [127].

Immune cells in cancer

Mitochondria are important in innate immune responses to cellular damage, stress and infection [128]. Mitochondrial dynamics might affect Toll-like receptor agonist-mediated inflammatory responses and immune cell polarization. One study reported that Toll-like receptor-regulated switching to mitochondrial fission in tumor-associated macrophages via ablation of the OMM protein FAM73b resulted in T cell activation and enhancement of antitumor immunity. In addition, mitochondrial morphology was found to alter Parkin expression and the activity of its downstream CHIP-IRF1 axis, revealing new potential targets for cancer immunotherapy [67]. In another study, T cells with decreased surface expression of the NADase CD38 exhibited intrinsically higher NAD+ levels, increased oxidative phosphorylation, and shifted mitochondrial dynamics that greatly enhanced tumor control [129].

Leukemia

Mesenchymal stem cells (MSCs) protect T cell acute lymphoblastic leukemia (T-ALL) cells against chemotherapeutic agents. Mitochondrial fragmentation was observed in T-ALL cells co-cultured with MSCs, and Drp1 phosphorylation on Ser616 was the underlying mechanism [130]. Leukemia stem cells (LSCs) are thought to be the driving factor of acute myeloid leukemia (AML) genesis and relapse after chemotherapy. Recently, depletion of Fis1 was demonstrated to attenuate mitophagy, resulting in cell cycle arrest and profound weakening of LSC self-renewal potential. Furthermore, inhibition of AMPK signaling rescued the biological effect of Fis1 loss [131].

Prostate cancer

Speckle-type POZ protein (SPOP) mutations contribute to prostate carcinogenesis. Experimental results demonstrated that expression of SPOP mutants augmented mitochondrial fission [132]. Furthermore, Drp1 expression promoted prostate cancer cell survival under metabolic stress conditions [78]. Recently, mitochondrial plasticity was found to be a new anticancer target in CSCs of human prostate cancer. BRD4 is one of extra-terminal domain BET proteins which bind to acetylated histones and transcription factors. Genetic knockdown of BRD4 blocked mitochondrial fission by repressing Mff and depleted CSCs. Ectopic expression of MFF rescued the exhaustion of CSCs [133].

Gastrointestinal cancers

Nestin was found to be upregulated in invasive gastrointestinal stromal tumor specimens. Knockdown of nestin inhibited the recruitment of Drp1 to mitochondria, thus changing mitochondrial dynamics [134]. In colorectal cancer, the release of high-mobility group box 1 protein promoted Drp1 phosphorylation, leading to chemoresistance [135]. Besides, Paris Saponin II exhibited antitumor capacity in colorectal cancer by modulating Drp1-mediated mitochondrial fission [136].

Conclusion

Great strides in the study of mitochondrial dynamics have been achieved in the past few years. Mitochondrial dynamics is particularly vital for the normal functions of mammalian cells. Indeed, as reviewed here, many kinds of human cancers are inextricably connected with dysregulated mitochondrial dynamics. In most cases, mitochondrial fission facilitates the proliferation, metastasis and drug resistance of cancer cells, causing cancer development. Inhibitors of mitochondrial fission effectors, such as Drpitor1 and Drpitor1a, have shown anticancer efficacy. However, in some cancers, mitochondrial fusion has been found to promote malignant phenotypes of cancer cells. Though current research achievements on the molecular mechanisms of mitochondrial dynamics have provided abundant therapeutic targets for cancer, means to achieve maximum benefit by manipulating mitochondrial dynamics in specific contexts need more investigation.

Furthermore, mitochondrial dynamics affects the proliferation of bulk cancer cells as well as the survival and stemness maintenance of CSCs, which are responsible for tumor recurrence and other malignant traits. Blocking mitochondrial fission weakens the self-renewal capacity of CSCs and leads to CSC exhaustion providing a new anticancer target. In addition, the function of immune cells such as T cells in the cancer microenvironment depends on tuning of mitochondrial fusion and fission, suggesting the feasibility of augmenting antitumor immunity by targeting mitochondrial dynamics.

Developing inhibitors against mitochondrial fusion and fission proteins is a promising new strategy to overcome resistance to chemotherapeutic drugs and cancer metastasis. However, few clinical trials of inhibitors targeting mitochondrial dynamics have been conducted to date, and much remains to be done before approaches targeting mitochondrial dynamics can be translated from the bench to the bedside.

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Disclosure of conflict of interest

None.

Abbreviations

MFN, Mitofusin; OMM, Outer mitochondrial membrane; OPA1, Optic atrophy protein 1; IMM, Inner mitochondrial membrane; PA, Phosphatidic acid; DRP1, Dynamin-related protein 1; ER, Endoplasmic reticulum; SNPH, Syntaphilin; SUMO, Small ubiquitin-like modifier; CL, Cardiolipin; PE, Phosphatidylethanolamine; PS, Phosphatidylserine; PISD, Phosphatidylserine decarboxylase; DAG, Diacylglycerol; ROS, Reactive oxygen species; PINK1, Phosphatase and tensin homologue (PTEN)-induced putative kinase 1; STX17, Syntaxin 17; MTDNA, Mitochondrial DNA; MICOS, Mitochondrial contact site and cristae organizing system; HCC, Hepatocellular carcinoma; MOMP, Mitochondrial outer membrane permeabilization; AURKA, Serine/threonine kinase Aurora A; MT-ND6, NADH-dehydrogenase 6; NSCLC, Non-small cell lung cancer; BTICs, Brain tumor initiating cells; AMPK, AMP-activated protein kinase; CDK, Cyclin-dependent kinase; RIN1, Ras Interactor 1; mTORC1, Mammalian target of rapamycin complex 1; MTFP1, Mitochondrial fission process 1; MSCs, Mesenchymal stem cells; T-ALL, T cell acute lymphoblastic leukemia; LSCs, Leukemia stem cells; AML, Acute myeloid leukemia; CSCs, Cancer stem cells; SPOP, Speckle-type POZ protein.

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