INTRODUCTION

Mitochondria are interconnecting and highly motile cellular organelles that undergo dynamic changes in response to physiological and pathological changes. These organelles are indispensable for maintaining proper cellular function, growth and development. During the lifetime of a cell, mitochondrial homeostasis requires a relatively stable equilibrium in a multitude of processes; namely, fission, fusion and biogenesis. Mitochondria form dynamic networks whose structure is molded by the opposing processes of mitochondrial fission and fusion (Figure 1). When the balance of the mitochondrial network structure is influenced by various cellular environmental stimuli, such as nutrient stress or viral attack, dramatic changes in the shape of mitochondria can occur. It has commonly been reported that mitochondrial morphology is closely associated with the ability of mitochondria to produce energy and mediate the mechanisms of cell death. Several proteins are involved in fission and fusion and are referred to as "mitochondria-shaping" proteins. These proteins include dynamin-related protein 1 (Drp1), mitofusin1/2 (Mfn1/2) and Optic atrophy 1 (OPA1), that have been implicated in mitochondrial shape changes are indispensable for autophagy, apoptosis and necroptosis. Drp1 is the main regulator of mitochondrial fission and has become a key point of contention. The controversy focuses on whether Drp1 is directly involved in the regulation of cell death and, if involved, whether it is a stimulator or a negative regulator of cell death. Here, we examine the relevance of the homeostasis of the mitochondrial network structure in 3 different types of cell death, including autophagy, apoptosis and necroptosis. Furthermore, a variety of cancers often exhibit a fragmented mitochondrial phenotype. Thus, the fragmented ratio can reflect tumor progression that predicts prognosis and therapeutic response. In addition, we investigate whether the targeting of the mitochondrial fission protein Drp1 could be a novel therapeutic approach.

KEYWORDS
cancer, dynamin-related protein 1, fission, fusion, mitochondrial network structure homeostasis
DRP1 from the cytoplasm to mitochondria. However, increasing Drp1 SUMOylation by knocking down SENP3 reduces the recruitment of Drp1 by Mff. The most common and important post-translational modification of Drp1 is phosphorylation. Indeed, multiple sites are phosphorylated by specific kinases and signaling pathways during mitochondrial fission. Different kinases drive the activities of Drp1 by phosphorylation on the GED domain, leading to relevant effects on the N-terminal GTPase and middle domains. In addition, activation or inhibition of Drp1 by phosphorylation mainly depends on the phosphorylation site involved. The 2 common and most important sites are serine 616 (Ser616) and serine 637 (Ser637). These 2 phosphorylation sites have opposite effects on the regulation of Drp1. Phosphorylation of Drp1 at Ser637 leads to the inhibition of mitochondrial fission, whereas phosphorylation at Ser616 results in promotion of fission.

2.2 | Mechanisms of mitochondrial fusion

Genetic studies in yeast and mammals have shown that cells with a high fusion-to-fission ratio (ie, more fusion than fission activity) possess very few mitochondria. These mitochondria are long and highly interconnected and function to maintain an adequate supply of nutrients within the cell. Mitochondrial fusion is a complex evolutionarily conserved process contributing to the mitochondrial network structure. Three large GTPase proteins have been shown to fuse and form various ultrastructures in the mitochondrial membrane. The IMM protein optic atrophy 1 (OPA1) interacts with the OMM proteins (Mfn1 and Mfn2) to form intermembrane protein complexes that couple the fusion of outer membranes to the inner membranes. Similar to the fission proteins, the abundance and activity of the fusion proteins can also be altered by post-translational modifications.

3 | The regulation of cell death by mitochondrial network structure homeostasis

To better adapt to ever-changing physiological conditions, mitochondrial network structure homeostasis cooperates with several important cellular processes, and especially those involving cell survival, including autophagy, apoptosis and necroptosis.

3.1 | Autophagy

Mitochondria play a paramount role in the mechanism of autophagy-induced cell death. Indeed, autophagy often occurs in mitochondria when they fail to maintain ATP levels, undergo starvation or are damaged. In many cases, autophagy can lead to greater generation of ROS and abnormal mitochondrial biogenesis, which will contribute to carcinogenesis. Therefore, there is no doubt that morphological characteristics determine the mitochondrial response to autophagy.
3.1.1 Mitophagy

The autophagic breakdown of mitochondria is termed mitophagy. Mitochondrial dynamics serve as filters to segregate morphologically and functionally damaged organelles from healthy ones. For example, fusion can reduce the sensitivity of damaged mitochondria to the lysosome for degradation, whereas mitochondria that undergo fission are split into shorter mitochondria. These smaller mitochondria are more easily consumed by autophagic membranes, leading to the formation of an autophagosome that targets damaged mitochondria to the lysosome. For instance, Parkinson’s disease (PD) is a common neurodegenerative disease in humans. Two genes, an E3 ubiquitin ligase (Parkin) and PTEN induced putative kinase 1 (Pink1), have been identified in hereditary PD, both of which are important for maintaining the integrity of the mitochondria. Pink1 stabilizes dysfunctional mitochondria and recruits the downstream molecule Parkin, whose activity is increased by translocation from the cytosol to damaged mitochondria. It induces ubiquitination and degradation of Mfn1/2 and can delay or inhibit fusion, leading to mitophagy.

3.1.2 Synergistic effect of fusion and fission in cell autophagy

Fission plays an important role in autophagy
Drp1 activation can disrupt the homeostasis of the mitochondrial network structure and impair mitochondrial function by inducing oxidative stress through increased production of reactive oxygen species (ROS). ROS induces damage of mitochondria and is correlated with an increase in the phosphorylation of Drp1 on Ser616 and mitochondrial fragmentation, activating autophagic cell death. In addition, knocking down Drp1 expression interrupts the balance of the mitochondrial network structure, blocking mitophagy, and affects mitochondrial quality, leading to ischemia/reperfusion injury. However, when faced with starvation or severe energy depletion-induced cell autophagy, lack of ATP can potentially activate fission through the elevation of ADP and AMP levels. On the one hand, ADP binding to the MID51 receptor is necessary for Drp1 recruitment and fission. On the other hand, AMP-sensing by energy sensor adenosine monophosphate-activated protein kinase (AMPK) results in phosphorylated Mff, leading to fission that induces autophagy.

Fusion plays a decisive role, similar to fission in autophagy
Elongated mitochondria can escape from degradation induced by autophagy by developing more cristae and upregulating ATP synthase dimerization and activity levels, thereby producing more ATP to maintain an adequate energy supply in the cells. Interestingly, the key protein involved in this process is Drp1. In this regard, protein kinase A (PKA) is activated by the rising cellular pool of cAMP, which is followed by phosphorylation of Drp1 at Ser637, leading to mitochondrial fusion and restoration of the level of ATP and increased cell viability. This hypothesis is supported by a recent study in which overexpression of mitochondrial inner membrane fusion protein OPA1 decreased mitochondrial fission, consequently preventing cell autophagy. Therefore, from these studies, we considered whether mitochondrial shape proteins can determine cell fate during autophagy (Figure 2).

**FIGURE 2** Fission and fusion regulate autophagy. Fission is controlled by the master regulator Drp1 and activation or inhibition of Drp1 by phosphorylation of Ser616 and Ser637, respectively. Drp1 shifts to the outer mitochondrial membrane (OMM) induced by recruitment of receptor proteins Mff and MID51. Red arrows: A shortage of energy results in increased levels of ADP, which can potentially activate fission by causing the binding of Drp1 to the MID51 receptor. AMP-sensing by AMPK results in phosphorylation of Mff, and similar to ROS induction of phosphorylation of Drp1 at Ser616 can activate mitochondrial fission followed by autophagy removing the damage mitochondria. Blue arrow: Energy shortage results in protein kinase A (PKA) activation, which is followed by phosphorylation of Drp1 at Ser637. This attenuates fission because the translocation of Drp1 to the OMM is inhibited. Meanwhile, fusion can reduce the sensitivity of damaged mitochondria to the lysosome for degradation. Finally, mitochondrial fusion and fission are contributed to homeostatic conditions.
3.2 | Apoptosis

At the mitochondrial level, proteins involved in mitochondrial network structure homeostasis dictate susceptibility to apoptosis.\textsuperscript{38,39} The critical event in the process of apoptosis is the increased permeability of the outer mitochondrial membrane, which triggers downstream cell death pathways by releasing cytochrome c and other pro-apoptotic factors from the intermembrane space into the cytosol.\textsuperscript{40}

3.2.1 | Fission and apoptosis

Based on the observed high fission-to-fusion ratio in apoptotic cells, fission is believed to be a necessary prerequisite for apoptosis.\textsuperscript{41} Overexpression of a Drp1-dominant-negative mutant (Drp1K38A) delays apoptosis, suggesting that Drp1 is required for cytochrome c release and caspase activation, which are basic characteristics of apoptosis.\textsuperscript{52} The observation that Drp1-deficient mice have the ability to resist apoptosis also supports a critical role for Drp1.\textsuperscript{43} In general, dephosphorylation of Drp1 (Ser637) by the phosphatase calcineurin promotes Drp1 movement from the cytosol to the mitochondrial outer membrane and induces mitochondrial fragmentation, which leads to apoptosis.\textsuperscript{44,45} This site is also phosphorylated by PKA and results in the inhibition of mitochondrial fission and increased resistance to apoptotic stimuli.\textsuperscript{46} This is mainly due to the movement of Drp1, which is a prerequisite for apoptotic signaling that is associated with cytochrome c release and caspase activities in vivo. Furthermore, studies also find that Drp1 cooperates with its mitochondrial OMM receptor proteins MID49/51, which are essential for cytochrome c release from mitochondria intracristae to cytoplasm.\textsuperscript{57,48}

In addition, remodeling of mitochondrial morphology can alter the activity of members of the Bcl-2 family, such as the BAX or BAK protein.\textsuperscript{49} Mitochondrial exhibition of numerous fragments reportedly determines the kinetics of apoptosis because Drp1 can permeabilize the MOM by enhancing the translocation of BAX to mitochondria.\textsuperscript{50} Importantly, anti-apoptotic Bcl-2 is essential for mitochondrial morphogenesis in healthy cells. One study showed that overexpression of Bcl-2 increases the average size of mitochondria.\textsuperscript{51} Together, the pro-apoptotic protein BAX and anti-apoptotic Bcl-2 interact with Drp1, which suggests an important crosstalk between the mitochondrial network structure and apoptosis.\textsuperscript{39,41,52}

Conversely, opposing evidence indicates that Drp1-mediated mitochondrial fission is an anti-apoptotic factor. The levels of total intracellular ATP are normal in Drp1-knockout mice during neural tube formation, but caspase 3 is activated, causing embryonic lethality by aberrantly inducing apoptosis.\textsuperscript{53} Depletion of the mitochondrial fission factor Drp1 and its inhibition by pharmacological agents increased apoptosis in human colon cancer cells and glioblastoma.\textsuperscript{34,55} This phenomenon has also been observed in human colon cancer cells. Blocking the activity of Drp1 led to mitochondrial membrane potential decreases and cytochrome c release, followed by apoptosis.\textsuperscript{54} Generally, inhibition of Drp1-regulated mitochondrial fission reduced cellular oxygen consumption and activated AMPK, thereby increasing apoptosis and decreasing tumor cell proliferation.\textsuperscript{55} This finding might provide further insight into the molecular mechanism of tumor suppression induced by inhibiting mitochondrial fission.

3.2.2 | Fusion mediates apoptosis

The anti-apoptotic effects of Mfn1 and Mfn2 have been attributed to a remodeling of the mitochondrial network.\textsuperscript{56} OPA1 and the pre-senilin associated rhomboid-like (PARL) have been shown to protect cells from apoptosis by controlling the reshaping of the mitochondrial cristae.\textsuperscript{57} In addition, research findings have shown that phosphorylation of Mfn1 by extracellular signal-regulated kinases (ERK) results in its inactivation. The inactivation of Mfn1 induces mitochondrial hyper-fragmentation, which results in increased sensitivity to apoptotic stimuli due to the oligomerization of BAK and its interaction with mitochondrial membranes.\textsuperscript{58}

In contrast to these views, fusion has also recently been shown to favor cell death and persistent mitochondrial fusion leads to robust caspase-dependent cell death.\textsuperscript{59} Studies show that the Mfn proteins mediate mitochondrial fusion and increase the sensitivity of cells to apoptosis.\textsuperscript{38,60} In bladder carcinoma, Mfn2 is considered to be a tumor suppressor gene, which is attributed to its anti-proliferation and pro-apoptotic activities.\textsuperscript{60} Similar to osteosarcoma, research findings suggest that Mfn1 significantly arrests cells in the G1/G0 phase, promotes apoptosis and triggers anticancer effects. Li et al (2014) found that miR-19b could target the 3′UTR sequences in the Mfn1 gene and downregulate the expression of the Mfn1 protein.\textsuperscript{38} A previous study clearly showed that BAX directly activates Mfn2 by interacting with its coiled-coil domain. In addition, Mfn2-dependent tethering of mitochondria to the endoplasmic reticulum (ER) improves sensitivity to apoptosis by uptake of calcium.\textsuperscript{61} In general, cellular deletion of pro-apoptotic proteins BAX and BAK results in relatively shorter and less fused mitochondria compared to healthy cells.\textsuperscript{62} Overall, mitochondrial fusion and fission play diverse roles in different cell lines under various physiological or pathological conditions.\textsuperscript{56,63} (Figure 3).

3.3 | Necroptosis

Necroptosis is an active and regulated form of programmed cell death.\textsuperscript{54,65} This process is typically initiated by classical pathways, such as Fas or tumor necrosis factor α (TNF-α) receptor combined with the inhibition of caspase activity, which results in the activation of receptor-interacting protein kinase 1 or 3 (RIP1 or RIP3).\textsuperscript{66} Importantly, the major characteristics of programmed necrosis include a crisis in ATP levels, ROS accumulation, calcium overload, and the opening of the mitochondrial permeability transition pore (MPTP).\textsuperscript{67} As mitochondria are the primary organelles in cells that supply energy and the major source of reactive oxygen species, they play a non-negligible role in the process of necroptosis.

3.3.1 | Is fission required for necroptosis?

Attention has focused on the importance of mitochondrial network structure homeostasis in necrosis and whether necroptosis could
Recent research findings have shown that necroptosis is associated with the mitochondrial fission protein Drp1. For instance, MLKL is thought to be associated with the regulation of mitochondrial fission through the phosphoglycerate mutase family member 5 (PGAM5) protein, which recruits Drp1 to the OMM by dephosphorylating its Ser637 site. Furthermore, Drp1 was shown to play a dispensable role in RIP3-induced necrosis. Indeed, knocking down Drp1 and overexpressing MLKL in murine embryonic fibroblasts caused cell death even in the presence of a broad-spectrum caspase inhibitor. These results indicate that necroptosis induced by RIPK3 requires MLKL but not Drp1. Overall, we could not determine whether Drp1 or fission is required for necroptosis and might be dependent on cell type and experimental conditions. Further work is required to determine how the components of mitochondrial fission and fusion actively participate in necroptosis (Figure 4).
4 | MITOCHONDRIAL NETWORK STRUCTURE IMBALANCE IS ASSOCIATED WITH CANCER

4.1 | Mitochondrial dynamics are biomarkers in cancer

Mitochondria are organelles that orchestrate a plethora of fundamental cellular functions that are associated with various steps of tumor progression. For example, mitochondrial energy metabolism intensifies proliferation and migration of cancer cells by increasing mitochondrial oxidative phosphorylation.\(^\text{75}\) In fact, cancer cells frequently show an imbalance of fission and fusion. Accumulating evidence is beginning to provide an increased mechanistic understanding of how mitochondrial dynamics, which reflect the organelles’ exquisite heterogeneity in shape and spatial distribution, affect tumorigenesis and participate in metabolic reprogramming.\(^\text{76,77}\) Consistent with these observations, many studies have shown that the mitochondria-associated fission protein Drp1 promotes tumor migration and pathogenesis, including in lung cancer,\(^\text{78}\) metastatic breast cancer,\(^\text{79}\) glioblastoma,\(^\text{55}\) colorectal cancer,\(^\text{80}\) pancreatic cancers,\(^\text{13}\) thyroid tumors,\(^\text{81}\) nasopharyngeal carcinoma\(^\text{5}\) and melanoma\(^\text{14}\) (Table 1).

4.2 | The Drp1-mediated signaling axis is involved in tumor cell survival

Similar to normal cells, the fate of cancer cells is closely related to mitochondrial morphology.\(^\text{5,71}\) In tumors, Drp1 is involved in mitochondrial fission and is regulated by specific kinases and signaling pathways, such as mitochondrial phosphatase PGAM5,\(^\text{69}\) AMPK,\(^\text{33}\) ERK\(^\text{13}\) and the cyclin-dependent kinase 1 (CDK1)/cyclin B1 complex.\(^\text{18,82}\) An interesting finding in HeLa cells suggested that mitochondrial phosphatase, PAGM5, can be activated by the RIPK1-RIPK3-MLKL complex and recruits Drp1 to the mitochondrial outer membrane, leading to a large number of ruptured mitochondria.\(^\text{69}\) Notably, Drp1 is a paramount regulator of mitochondrial metabolism that contributes to oncogenic Ras-induced cellular transformation and cancer development.\(^\text{14}\) Generally, oncogenic Ras activates ERK, followed by phosphorylation of Drp1 at Ser616. Eventually, this orchestrated cascade leads to mitochondrial Drp1 activation and promotion of mitochondrial fission in human pancreatic cancer, driving tumor growth.\(^\text{13}\) Another study showed that Mff can be phosphorylated directly by AMPK. Subsequently, recruitment of Drp1 from the cytosol to the mitochondrial outer membrane results in mitochondrial fission.\(^\text{32}\) Progress in cell cycle is mainly regulated by members of the CDK family when bound to their respective cyclin partner.\(^\text{83}\) Overexpression of cyclin B1 promotes G2/M phase transition, resulting in uncontrolled cell proliferation and even malignant transformation.\(^\text{84}\) In HeLa cells, the CDK1/cyclin B1 complex upregulates the phosphorylation of Drp1 (Ser616) and promotes mitochondrial fission, accelerating the progression of cancer.\(^\text{18}\)

4.3 | Utilization of mitochondrial dynamics or the fission protein Drp1 as therapeutic targets in cancer

Mitochondrial dynamics can be used to divide cancers into categories, which play an important role in predicting prognosis and treatment response in the clinical setting.\(^\text{13,79,81,85}\) Human lung cancer cell lines often exhibit an imbalance of mitochondrial network structure homeostasis (ie, more fission than fusion) and this phenotype can be reversed by Drp1 inhibition or Mfn2 overexpression

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**TABLE 1** Mitochondrial fission protein Drp1 and tumors

| Cancer types          | Effects on Drp1                  | Functions                                      | Key references |
|-----------------------|----------------------------------|------------------------------------------------|----------------|
| Lung cancer           | Inhibition of Drp1               | Prevents cell cycle progression                | 78             |
| Breast cancer         | Enhanced the expression of Drp1  | Increased cancer cell migration and invasion   | 79             |
| Glioblastoma          | Activation of Drp1               | Correlated with poor prognosis in glioblastoma | 55             |
| Colon cancer          | Downregulation of DRP1           | Decreased proliferation and increased apoptosis of these cells | 74             |
| Nasopharyngeal carcinoma | Decreasing the activity of Drp1 | Inhibits the stemness                          | 5              |
| Oncocytic Thyroid Tumors | Upregulation of Drp1            | A feature of tumor malignancy and increased cancer cell migration | 81             |
| Pancreatic cancers    | Knockdown of Drp1                | Inhibits tumor growth                          | 13             |
| Melanoma              | Loss of Drp1                     | Prevents RASG12V-induced mitochondrial dysfunction and resistant to transformation | 14             |
to promote cell cycle arrest\textsuperscript{78} and increase spontaneous apoptosis that could provide promising novel therapeutic strategies.\textsuperscript{54} In addition, in brain tumor-initiating cells, inhibition of Drp1 upregulates the expression of AMP-activated protein kinase, resulting in decreased migration and proliferation of tumor cells.\textsuperscript{55} Xie et al (2015) also showed that patients with high levels of phosphorylated Drp1 (Ser616) exhibit a poor survival rate in a clinical glioblastoma tissue analysis.\textsuperscript{55} A recent study indicates that mitochondrial cyclooxygenase 2 (COX-2) interacts with p53 to activate Drp1. The natural compound resveratrol (RSV) combined with 5-fluorouracil (5-FU) increased the sensitivity of nasopharyngeal cancer (NPC) to chemotherapy and lowered the stemness of NPC by suppressing the activity of Drp1.\textsuperscript{5} Another report showed that upregulating Drp1 and silencing Mfn1 was accompanied by a fragmented mitochondrial phenotype and enhanced invasive and metastatic abilities of breast cancer cells.\textsuperscript{79} Furthermore, Mdivi-1 has been considered to be a small-molecule inhibitor of mitochondrial fission that specifically targets Drp1. Recent research has reported that Mdivi-1 also targets mitochondrial complex I in the absence of Drp1, and inhibits ROS production in ischemia-reperfusion injury disease models.\textsuperscript{86} In a cancer model, Mdivi-1 induced cell death in vitro, suggesting that Mdivi-1 inhibited mitochondrial fission resists cancer cell survival.\textsuperscript{5,55} Thus, the above studies support the idea that inhibition of mitochondrial fragmentation in cancer\textsuperscript{5,80,81} might be used as a therapeutic strategy to overcome metastasis and chemoresistance.

5  \textbf{FUTURE PERSPECTIVES}

Mitochondrial network structure homeostasis is crucial for maintaining a healthy mitochondrial population. Under normal and pathological conditions, various factors determine mitochondrial shape, consequently triggering a series of signal transduction and molecules involved in the regulation of multiple forms of cell death. Cancer is a disease associated with mitochondrial dysfunction and experimental evidence suggests that utilizing mitochondrial dynamics as a therapeutic strategy or biomarker in cancers might be appropriate. Targeting the mitochondrial fission protein Drp1 or other shaping proteins has become a topic of interest. Further studies are needed to understand the differential effects of oncogenic signaling pathways on mitochondrial dynamics and to identify additional new signaling axes that regulate mitochondrial network structure homeostasis.

DISCLOSURE

No competing financial interests exist.

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