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Review

Mitochondrial dynamics and cancer

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ABSTRACT

Mitochondrial morphology is regulated by continuous fusion and fission events that are essential for maintaining a normal mitochondrial function. If the last years have witnessed major discoveries in the characterization of the fission and fusion machineries, little is known about the physiological role of mitochondrial dynamics. In this review we report the results showing evidences of relationships between mitochondrial dynamics and cellular metabolism, autophagy or apoptosis. We discuss how different mitochondrial alterations observed in cancer cells could be linked to unbalanced mitochondrial fission or fusion events and how this could impinge on key essential cellular processes, thereby contributing to tumorigenesis.

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Mitochondria are dynamic, semi-autonomous organelles surrounded by a double membrane that have their own genome and protein synthesis machinery. They are motile and undergo frequent changes in number and morphology through fusion and fission events. In addition to being the major source of ATP in eukaryotes, they are the site of many important metabolic reactions such as the urea cycle, lipid metabolism, steroid hormone and porphyrin synthesis and interconversion of amino acids. Moreover, mitochondria play a central role in complex physiological processes including cellular proliferation, differentiation, apoptosis [1,2] and in cellular processes like glucose sensing/insulin regulation [3], cellular $Ca^{2+}$and ROS (reactive oxygen species) homeostasis [4–7]. It is therefore not surprising that mitochondrial dysfunctions have been found to be associated with several diseases such as degenerative diseases, aging and cancer [8,9]. Many cancer cells are characterized by a decrease in oxidative phosphorylation and by a high glycolytic activity, as first described 80 years ago by Warburg [10]. Therefore, many cancer cells mainly use glucose, even in the presence of oxygen, a phenomenon called "aerobic glycolysis". Moreover, mitochondria are at the core of the so-called intrinsic apoptotic pathway and appear to be protected in cancer cells explaining, at least in part, cell tumorigenesis. Proteins involved in the fusion/fission machinery were recently found to regulate the intrinsic apoptotic pathway and therefore could participate in the resistance of cancer cells to apoptotic stimuli. Moreover, shaping of mitochondria could have impacts on mitochondrial function and cell metabolism. In this review we report data from the literature addressing the role of mitochondrial dynamics in mitochondrial function, cell metabolism and apoptosis and we will discuss the possibility that a defect in the mitochondrial fusion or fission machinery may have an impact on tumorigenesis.

1. Proteins involved in mitochondrial dynamics

This review will be focused on the proteins involved in the fusion and fission of mitochondria (Fig. 1). We will not describe the mechanisms that allow mitochondria to move in the cell.

1.1. Mitochondrial fusion

The mitochondrial fusion apparatus involves two proteins conserved from yeast to human: the large outer membrane GTPase, Fuzzy onion/Mitofusin, and the inner membrane dynamin-like Mgm1p/Opa1 [2]. In mammals, two mitofusins, Mfn1 and Mfn2, have been described, that hydrolyse GTP with a different efficacy [11], suggesting a different function. These proteins dimerize via their coiled domain, allowing mitochondrial tethering and fusion (Fig. 1). On the other hand, Mgm1p/OPA1 is required for fusion of the inner membrane, mtDNA maintenance and cristae morphology [12,13]. The role of this protein in cristae organization could be mediated by the ATP synthase whose oligomerization appears to have an impact on inner membrane curvature and cristae biogenesis [14–17]. In mammals, there are at least eight isoforms of OPA1, produced by alternative splicing and proteolytic processing by mitochondrial proteases, yet the role of these isoforms is unclear. Other proteins have been reported to play a role in mitochondrial fusion such as Mitofilin which is involved in cristae morphology [18], MitoPLD a mitochondrial phospholipase D [19] and recently mitochondrial morphology and cristae structure (MICS1) an inner

Abbreviations: OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; MFN, mitofusin; CMT, Charcot–Marie tooth; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

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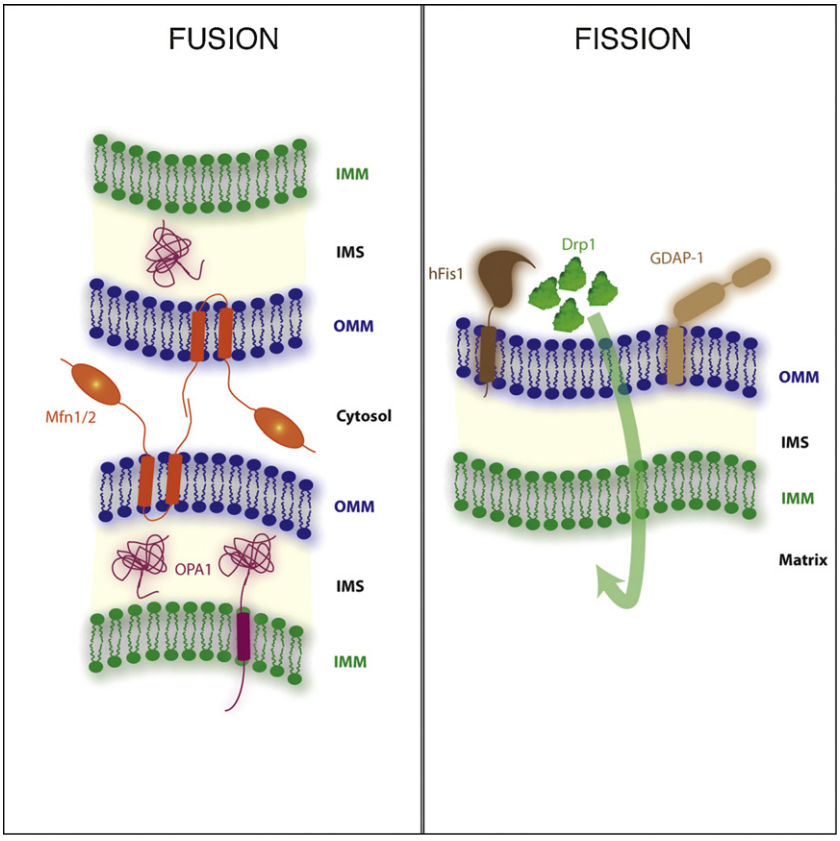

Fig. 1. Proteins involved in the fission and fusion of mitochondria. Left panel: Mfn1 and 2 are responsible for tethering and fusion of the outer mitochondrial membranes whereas OPA1 is responsible for the fusion of the inner membrane. How the fusion of the outer and inner membranes is coordinated is still unclear. Right panel: Drp1 can be recruited at the surface of mitochondria through binding to Fis1. Then the protein forms a ring around mitochondria leading to its fission.

membrane protein necessary for maintenance of mitochondrial morphology in specific cristae structures [20]. Finally, the β-subunit of the protein phosphatase 2A (PPA2) has also been involved in mitochondrial dynamics [21]. The mechanisms that coordinate fusion of the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM) are still unclear.

1.2. Mitochondrial fission

Mitochondrial division is orchestrated by multi-component protein machineries that were first described in yeast [22]. In mammals, the key molecules of the mitochondrial fission process are hFis1 and Drp1 (Dynamin related protein 1). The hFis1 protein is integrated in the OMM and serves as a receptor for Drp1 which translocates from the cytosol to the OMM where it forms a ring that drives fission of the organelle by a still unclear mechanism (Fig. 1). However, in many cases Drp1 does not seem to require Fis1 to bind mitochondria [23]. In yeast, two adaptors Caf4p and Mdv1p cooperate with Fis1 to recruit Drp1 [24–26]. No homolog of these proteins has been identified in mammals. Besides Drp1 and Fis1, the mitochondrial membrane proteins MTP18 [27,28], ganglioside-induced differentiation associated protein 1 (GDAP1) [29] as well as Miro-1 and Miro-2 (Mitochondrial Rho-GTPase) [30,31] are also involved in mitochondrial fission.

2. Regulation of the fission and fusion of mitochondria

2.1. Post-translational modifications of proteins involved in mitochondrial fission and fusion

Components of the fission and fusion machinery have been shown to be regulated at the post-translational level through phosphorylation, ubiquitination and sumoylation.

Phosphorylation has been reported to control Drp1's activity. Cdk1/cyclin B protein kinase can phosphorylate and activate Drp1 thereby promoting a transient mitochondrial fission at the onset of mitosis [32]. In contrast, phosphorylation of Drp1 by cAMP-dependent protein kinase (PKA) inactivates the GTPase activity of Drp1, resulting in mitochondrial fusion [33]. This phosphorylation can be reversed by the serine/threonine phosphatase calcineurin leading to mitochondrial fission [34].

The E3 ubiquitin ligases, MARCH-V (membrane-associated ring finger (C3HC4) 5) (also called MITOL), PARKIN and MULAN (Mitochondrial Ubiquitin Ligase Activator of NF-κB), have also been identified as regulators of mitochondrial dynamics [35–38]. MARCH-V is able to bind and to modify Drp1's activity resulting in a change of mitochondrial shape. However, as MARCH-V has been characterized as an inhibitor and an activator of fission [35,36,39], its function needs to be clarified. Recent data have demonstrated that PARKIN promotes mitochondrial fission and is involved in the selective elimination of impaired mitochondria by autophagy [37,40]. MULAN was first identified as an activator of NFκB. This effect, together with its localization at the mitochondria and its impact on mitochondrial morphology [38], provide a link between mitochondrial dynamics and mitochondria-to-nucleus signaling.

In addition to phosphorylation and ubiquitination, sumoylation also influences Drp1 function. SUMO1 and its conjugating enzyme Ubc9 can stabilize Drp1 at the mitochondrial membrane recruitment sites, thereby driving mitochondrial fission [41]. Interestingly during apoptosis, Drp1 is sumoylated in a Bax/Bak-dependent manner [42]. Moreover, the use of SENP5, a SUMO protease reverses this SUMO1-induced fragmentation [43]. If most of these examples concern post-translational modifications of Drp1, several evidences suggest that other proteins involved in the fission and fusion of

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