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Regulators of mitochondrial dynamics in cancer

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Mitochondrial dynamics encompasses processes associated with mitochondrial fission and fusion, affecting their number, degree of biogenesis, and the induction of mitophagy. These activities determine the balance between mitochondrial energy production and cell death programs. Processes governing mitochondrial dynamics are tightly controlled in physiological conditions and are often deregulated in cancer. Mitochondrial protein homeostasis, transcriptional regulation, and post-translational modification are among processes that govern the control of mitochondrial dynamics. Cancer cells alter mitochondrial dynamics to resist apoptosis and adjust their bioenergetic and biosynthetic needs to support tumor initiating and transformation properties including proliferation, migration, and therapeutic resistance. This review focuses on key regulators of mitochondrial dynamics and their role in cancer.

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Mitochondrial dynamics: regulation and physiological relevance

Mitochondria are dynamic organelles that form filamentous networks or appear as fragmented, rounded structures within cells. These morphologies continuously change as a result of coordinated fission (fragmentation), fusion (elongation), or movement along microtubular structures [1,2]. Fusion and fission are highly conserved processes, orchestrated by dynamin related GTPases: in mammals, cytosolic dynamin related protein (Drp1), is recruited to mitochondria and executes mitochondrial fragmentation (fission) after undergoing extensive post-translational modification (Table 1). Drp1 binds to receptor/adaptor proteins (such as Fis1, MFF, MiD49, and Mid51), at the mitochondrial outer membrane (MOM), and oligomerizes to form a ring-like structure along the MOM that divides mitochondria by constriction. Such sites are marked by tubules from the endoplasmic reticulum (ER) that 'pre-constrict' mitochondria before Drp1 recruitment [1,2]. Two GTPases, mitofusin 1 and 2 (MFN1/2), reportedly mediate MOM fusion, whereas the inner mitochondrial membrane (MIM), is subsequently fused by a process involving the cristae-shaping protein OPA1. Fusion machinery proteins are also subject to posttranslational modifications that regulate their abundance and activity (Table 1).

Although the molecular machinery that shapes mitochondrial morphology is well described, its relationship to mitochondrial functions (such as ATP generation, amino acid and lipid biosynthesis and breakdown, ROS generation, and Ca^{2+}-signaling) is still under evaluation (Figure 1). Mitochondrial shape is particularly plastic during cell cycle progression. Highly connected mitochondria seen in G1/S, are thought to ensure sufficient ATP production during energy-consuming cell proliferation [3], whereas fission increases during S/G2/M as a means to distribute mitochondria equally among daughter cells [4]. In post-mitotic cells, extensive mitochondrial fragmentation occurs during apoptosis [1,2], and the mitochondrial network responds to changes in nutrient or oxygen supply, linking mitochondrial dynamics to cellular signaling pathways and stress responses [5,6,7,8••]. Linked to their role in mitochondrial morphology and function, regulators of mitochondrial dynamics are associated with cytoskeletal proteins and with other cellular organelles. For example, MFN2 tethers mitochondria to the ER and modulates lipid metabolism, calcium homeostasis, and the ER stress response [9]. Mitofusins also link mitochondria to kinesin motors by direct interaction with Miro/Milton, thereby influencing mitochondrial transport [1].

Genetic inactivation of any core mitochondrial-shaping protein promotes embryonic lethality in mice, indicating that mitochondrial dynamics are indispensable for life [10–12]. Whether the perturbation of mitochondrial dynamics per se, or some of the altered processes associated with these dynamics are the cause for the lethality, remain to be determined. In humans, mutations in core proteins have been reported and are associated with tissue-restricted diseases: for example, optic atrophy, in which the loss of retinal ganglions and optic nerve degeneration is linked to OPA1 mutations; Charcot-Marie-Tooth disease type 2A, which is characterized by axonal degeneration of peripheral nerves, results from MFN2 mutations. These observations suggest that altered mitochondrial dynamics and integrity has distinct implications in different cell

Table 1

Post-translational modifications of mammalian mitochondrial dynamics proteins

Substrate	Regulator	Signal	Effect	Comment	Refs
Drp1	CDK1	P	Activation	Induces fission during mitosis; Aurora A kinase mediates Drp1 recruitment to mitochondria via phosphorylation of RALA.	[4,66]
	CDK5	P	Activation	Increases fission; important for maintenance of glioblastoma stem-like cells	[43••]
	ERK1/2	P	Activation	RAS^{G12V}-mediated transformation depends on Drp1 activity. Drp1 is essential for MAPK-driven tumors	[8••,38••]
	PKCδ	P	Activation	Increases fission upon oxidative stress; contributes to encephalopathy in rats	[67]
	PKA	P	Inactivation	Limits mitophagy under nutrient starvation; Inhibited under hypoxia to increase apoptosis in cardiomyocytes	[5,26,68]
	CAMKI	P	Activation	Increases Drp1 recruitment and association with Fis1	[69]
	CAMKII	P	Inactivation	Inhibits Drp1 activity; indicative for differentiation in glioblastoma	[43••]
	Rock1	P	Activation	Induces fission under hyperglycemia	[70]
	Calcineurin	De-P	Activation	Reverses PKA-mediated inhibitory phosphorylation	[68]
	NO	S-nitro	Activation	Increases fission in response to β-amyloid; contributes to neuronal damage; controversial	[71,72]
	O-GlcNAc transferase	O-GlcNAc	Activation	Activates fission under high glucose; co-incides with decrease in S637 inhibitory phosphorylation	[73]
	MAPL	SUMO	Activation	Bax/Bak dependent, stabilizes ER-mitochondria contact, required for efficient cytochrome c release	[32••]
	SENP5	De-SUMO	Inactivation/ stabilization	Decreases fission and ROS; increases fission during mitosis by stabilizing oligomerization	[74,75]
	SENP3	De-SUMO	Activation	Increased cytochrome c release under neuronal ischemia/reperfusion	[76]
	March5	Ubi	Degradation	Mediates proteasomal degradation of Drp1; essential for Drp1-mediated fission	[56,59]
	Parkin	Ubi	Degradation	Mediates proteasomal degradation of Drp1; implications in Parkinsons disease	[44]
	APC/C	Ubi	Degradation	Mediates proteasomal degradation of Drp1 during M/G1 transition	[77]
MFN1	ERK	P	Inactivation	Inhibits fusion, increases apoptosis through BAK activation	[78]
	HDAC6	De-AC	Activation	Increases fusion actively under glucose deprivation; more severe starvation increases fusion passively by PKA-mediated inhibition of Drp1	[79•]
	March5	Ubi	Degradation	Targets acetylated Mfn1 more efficiently; prevents Mfn1 accumulation and cell death under mitochondrial stress conditions	[58]
MFN2	PINK1	P	Signaling	Fusion-independent role, serves as Parkin receptor at mitochondria	[18]
	JNK	P	Signaling	Marks MFN2 for HUWE1-dependent ubiquitination; inhibits fusion under stress conditions; senses shortage of stearic acid	[80,81••]
	HUWE1	Ubi	Degradation	Marks phosphorylated MFN2 for degradation; inhibits fusion under stress conditions	[80,81••]
	March5	Ubi	Activation	Fusion-independent role; increases mitochondria-ER tethering	[64••]
MFN1/2	Parkin	Ubi	Degradation	Prevents fusion to isolate mitochondria for mitophagy	[82,83]
	USP30	De- Ubi	Inactivation	Limits fusion without altering protein abundance. Similar mechanisms reported in yeast: SCF^{Mdm30} activates fusion by ubiquitination of Fzo1, which is counteracted by UBP12	[24•,84]

P: Phosphorylation; **De-P**: Dephosphorylation; **S-nitro**: S-nitrosylation; **O-GlcNAc**: O-GlcNAcylation; **SUMO**: SUMOylation; **De-SUMO**: De-SUMOylation; **De-AC**: De-Acetylation;

types. Accordingly, perturbations in the balance between fusion and fission have been linked to neurodegenerative and cardiovascular diseases [13,14], and its implication in cancer will be discussed here.

Mitochondrial dynamics, mitochondrial quality control and cell fate decision

Given the importance of mitochondria for vital processes, several mechanisms serve to maintain their integrity [15]. First, accumulation of damaged proteins in mitochondrial compartments causes transcriptional upregulation of proteases and chaperones, which restore homeostasis by clearing aberrant proteins from the organelle. Additionally, ubiquitin-dependent proteasomal degradation of mitochondrial proteins contributes to mitochondrial quality control (QC). Third, mitochondria-derived vesicles have been demonstrated to carry specific cargo and fuse with the lysosome, providing an additional route to remove molecules from mitochondria [15]. Failure of any of these pathways to maintain homeostasis, results in elimination of the entire mitochondria via mitophagy, or, if stress is sustained, in apoptosis [2].