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Regulators of mitochondrial dynamics in cancer

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Abstract

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.

Graphical abstract

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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 [5–8**]. 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 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].

Mitochondrial quality control and cell fate decisions

Among the best-studied regulators of mitochondrial QC, are the ubiquitin ligase Parkin, and the serine threonine kinase Pink1 [1]. Under non-stressed conditions, PINK1 is continuously imported into the mitochondrial intermembrane space, and processed by proteases. PINK1 cleavage products are released into the cytosol and degraded by the proteasome. Upon loss of mitochondrial membrane potential, cleavage is abrogated, PINK1 accumulates in the MOM, undergoes autophosphorylation, and subsequently, PINK1 phosphorylates ubiquitin, MFN2, and Parkin [1]. Phosphorylated ubiquitin serves as a recognition signal for autophagy receptors (OPTN and NDP52), and is sufficient to induce mitophagy, independent of Parkin [16**]. Pink1-mediated phosphorylation of both, Parkin and ubiquitin, is required for Parkin E3-ligase activity [17**]. Phosphorylated MFN2 recruits Parkin to depolarized mitochondria, identifying MFN2 as a Parkin receptor [18]. Parkin-mediated ubiquitination of MOM proteins amplifies initial mitophagy signals, and recruits additional autophagy receptors to the damaged organelle [16**]. Parkin-mediated ubiquitination also targets MOM proteins for proteasomal degradation, among which are MFNs, resulting in inhibition of fusion, and consequently, isolation of dysfunctional mitochondria from the network [19]. Interestingly, the kinesin adaptor Miro is also target of Parkin-mediated degradation, which arrests mitochondrial motility, further separating damaged mitochondria [1].

The PINK1/Parkin axis functions in mitochondrial QC on several levels, and, dependent on the degree of stress, triggers adaptive responses before the entire organelle is removed (Figure 2). Under moderate stress conditions PINK1 and Parkin reportedly regulate generation of mitochondria-derived vesicles to degrade oxidized mitochondrial components [20]. Similarly, low dose treatment with the mitochondrial uncoupler CCCP results in Parkin-mediated fusion, which limits mitochondrial damage and thus mitophagy in neurons [21] (see next paragraph). Higher doses of CCCP reportedly promote Parkin recruitment and mitophagy, which is antagonized by Parkin interaction with antiapoptotic Bcl-2 proteins (Bcl-xL, Mcl-1, Bcl-w) [22**]. Given that mitophagy serves as a QC mechanism to remove damaged mitochondria and is thought to prevent cell death, inhibition of mitophagy by antiapoptotic proteins appears counterintuitive, unless that inhibition primes mitochondria for induction of apoptosis. Indeed PINK1/Parkin promote mitochondrial depolarization-

induced apoptosis by ubiquitinating and targeting antiapoptotic Mcl-1 for degradation [23**]. Reciprocal activity between Parkin and the Bcl-2 family proteins represents a regulatory node that shifts homeostatic responses towards cell death when mitochondrial stress is sustained. Parkin-mediated effects are further regulated by de-ubiquitinating enzymes, such as USP30 and USP35, which reportedly de-ubiquitinate Parkin substrates to antagonize mitophagy [24*] or Parkin-dependent cell death [25*].

Fusion and fission cycles link mitochondrial quality and apoptosis

Mitochondrial fusion and fission are both implicated in mitochondrial QC (Figure 2). Fusion is thought to dilute damaged mitochondrial molecules, such as oxidized lipids or proteins, or mutated mitochondrial DNA [2]. Fusion also reportedly spares mitochondria from autophagy activated under nutrient starvation [6,26]. MFN2-dependent tethering of mitochondria to the ER increases upon fusion, enhancing lipid and calcium transfer between organelles [27], but simultaneously increases sensitivity to calcium-dependent apoptosis [28,29]. Fission in turn is critical for mitophagy by generating one depolarized and one hyperpolarized mitochondrion. This asymmetric fission enables the removal of the depolarized mitochondrion, whereas the hyperpolarized can be re-introduced into the healthy mitochondrial network [30].

The interplay between mitophagy, mitochondrial dynamics, and cell death, serves to maintain mitochondrial integrity in response to stress. As fragmented mitochondria appear in apoptosis, fission is suggested to be an integral step of the apoptotic cascade. Indeed, Drp1 knockout mice display defects in neural tube closure, associated with impaired degree of apoptosis. However, MEFs isolated from these mice respond to apoptotic signals similarly to control MEFs, although cytochrome c release is delayed [11,12], indicating that the consequence of impaired fission on apoptosis is context-dependent. Instead of a strict association between apoptosis and fission, adjustment of mitochondrial shape reportedly modifies the ability of Bax to permeabilize the MOM [31**]. Whereas extensive fission inhibited ER stress-mediated apoptosis in MFN1-deficient cells, restoration of mitochondrial membrane curvature by pharmacological inhibition of Drp1 facilitated cell death [31**]. This observation is in line with the fact that fission per se does not induce apoptosis, and demonstrates that the activity of pro-apoptotic factors depend on the remodeling of mitochondrial shape to efficiently promote apoptosis [31**]. Similarly, MAPL-dependent SUMOylation of Drp1, stabilizes ER-mitochondrial contacts, and facilitates BAX/BAK-dependent cytochrome c release following apoptotic signals [32**]. Inhibition of MAPL delays apoptosis but does not prevent cell death, further indicating that the remodeling of mitochondrial shape modifies the activity of Bcl-2 proteins and determines apoptosis kinetics.

Similar to the interplay of Bcl-2 family proteins and Parkin, alterations in mitochondrial dynamics also mediate calcium-dependent apoptosis, which is enhanced in highly interconnected mitochondria [28,29]. In this context, Mcl-1S, a Mcl-1 splice variant that displays proapoptotic activity, facilitates Ca^{2+} -dependent apoptosis by interfering with Drp1 recruitment to mitochondria, allowing unopposed fusion [28]. Thus, distinct pathways merge

on the mitochondrial dynamics machinery to modulate network architecture, which either restores homeostasis, or, depending on the type and degree of damage, execute cell death.

Mitochondrial dynamics and cancer

Cancer cells often exhibit fragmented mitochondria; moreover, high expression or enhanced activation of Drp1 and/or downregulation of MFN2, mediate this phenotype in lung cancer [33], metastatic breast cancer [34**], glioblastoma [35], neuroblastoma [36], colorectal cancer cells [37], pancreatic cancers [38**] and melanoma [8**]. Enhanced fission or reduced fusion is linked to several cancer-related phenotypes, and reversal of this phenotype by Drp1 inhibition or MFN2 overexpression, promotes cell cycle arrest [33] and increased spontaneous apoptosis [33,37]. Mitochondrial fragmentation with a concomitant decrease in complex I activity following survivin overexpression, enhances glycolysis, limits ROS accumulation, and decreases the response to cytotoxic therapies [36]. Although most studies reported fragmented mitochondria in cancer cells, interconnected mitochondria are observed following changes in glucose availability [7], or in response to anticancer therapies such as MAPK- or PI3K-inhibitors [8**,38**,39**]. These observations are evidence that the dynamics machinery remains intact in cancer, and could contribute to homeostatic adjustments under oxygen/nutrient shortage, or in response to therapeutic interventions.

Ras-induced transformation depends on fission

Two independent studies demonstrate that MAPK signaling, which is commonly activated in cancer, activates Drp1 via ERK-mediated phosphorylation, and that Drp1 activity is crucial for Ras-driven transformation [8**,38**]. Drp1 activity is essential for pancreatic cancer growth in xenograft experiments [38**]. Notably, Drp1 contributes to Ras-induced mitochondrial reprogramming, which is characterized by decreased membrane potential, oxygen consumption, and ATP synthesis, and increased ROS [8**]. In melanoma, the BRAF^{V600E}-mutation correlates with Drp1 phosphorylation, whereas MAPK-inhibition reverses Drp1-mediated mitochondrial fragmentation, improves mitochondrial function, and sensitizes cells to mitochondria-targeting drugs [8**].

Mitochondrial QC and cancer

Besides Pink1/Parkin, several proteins are implicated in control of mitophagy [40]. In brief, NIX, BNIP3 and FUNDC1 are MOM proteins, which serve as autophagy receptors in an ubiquitin-independent manner. Furthermore, the phospholipid cardiolipin can initiate mitophagy. Finally, ubiquitin ligases, such as SMURF1 (although independent of its UBL activity), and MAPL can induce mitophagy. Thus, although Parkin is frequently inactivated genetically in cancer [41], mitophagy can occur in cancer cells lacking Parkin activity, and related phenotypes might be mediated by mitophagy-independent Parkin function.

How might cancer cells benefit from Parkin loss? Since Parkin harbors proapoptotic function, and cancer-associated mitochondrial dysfunction/reprogramming is linked to mitochondrial fragmentation and elevated ROS production, Parkin loss could increase resistance to mitochondria-induced apoptosis. Increased expression of Drp1 and Mcl-1,

which are targeted for degradation by Parkin and often overexpressed in cancer, support this idea.

Notably, Drp1-dependent fission reportedly functions in stem cell maintenance in immortalized mammary epithelial stem-like cells [42**]. Labeling of “old” mitochondrial proteins revealed that, upon asymmetric cell division, stem-like cells contained a greater number of “new” mitochondria, whereas cells containing more “aged” mitochondria were less efficient in mammosphere formation and, possibly through increased ROS, primed to differentiate. Interfering with Drp1 or Parkin activity abrogated asymmetric distribution of mitochondrial content and reduced stem-cell properties in vitro [42**]. Although these results await confirmation in adult stem cells in vivo, they suggest that mitochondrial fitness regulates stemness. Interestingly, high Drp1 expression and mitochondrial fragmentation contribute to maintenance of brain tumor-initiating cells (BTICs) [43**]. Although expression of a constitutive-active Drp1 mutant is not sufficient to reprogram non-BTICs into tumor-initiating cells, Drp1 activity is required to maintain their tumorigenic potential and prevent AMPK-driven apoptosis [43**]. As Parkin is inactivated in glioma [41], Parkin-independent mitochondrial QC may contribute to BTIC maintenance. As Parkin reportedly destabilizes Drp1 [44], its loss in cancer cells may contribute to stemness by upregulating Drp1.

Mitochondrial dynamics are implicated in cancer cell migration

Emerging evidence supports a role for mitochondrial dynamics in tumor cell migration in glioblastoma and breast, lung or prostate cancer [34**,45–48]. These studies suggest that, similar to activities reported in neurons, mitochondria are trafficked to sites of high-energy demand. In migrating cancer cells, mitochondria accumulate at the leading edge, where processes requiring high energy, as focal adhesion dynamics, occur. Interfering with the mitochondria/microtubule linkage via knockdown of the Rho-GTPase Miro1 inhibits mitochondrial trafficking and reduces cancer cell migration [46]. Most studies report fission as a prerequisite for efficient relocation of mitochondria, and upregulation/activation of Drp1 or downregulation/inactivation of MFN1 is observed in invasive cancer cells [34**, 45,47,48]. Although Caino and colleagues [39**] observed similar mitochondrial redistribution to the leading edge of migrating glioma cells following PI3K inhibition, mitochondria displayed an elongated phenotype. MFN1 downregulation abolished mitochondrial trafficking and abrogated the migratory response. Thus, mitochondrial dynamics are linked to cancer cell migration, and the relative contribution of fission or fusion appears to be context-dependent. Interestingly, hypoxia is considered a major driver of metabolic reprogramming, tumor progression, and metastasis [49]. We previously established a link between hypoxia and increased fission: Siah2 (a hypoxia-responsive ubiquitin ligase) targets the mitochondrial scaffolding protein AKAP121 for proteasomal degradation, resulting in decreased PKA-dependent inhibitory phosphorylation of Drp1, and thus active fission [5]. Two recent studies link mitochondrial fission to hypoxia-induced migration of breast cancer [50] and glioblastoma [35] cells. Given the importance of hypoxia to tumor progression, further evaluation of the link between mitochondrial dynamics and hypoxia-driven phenotypes is required.

Ubiquitin ligases as emerging regulators of mitochondrial dynamics in cancer

The role of ubiquitin in regulating mitochondrial dynamics and mitochondrial QC has recently been reviewed [51,52], and proteolytic and non-proteolytic functions of ubiquitin-modifications in mitochondrial dynamics are summarized in Table 1. Above, we summarized Parkin function in regulating mitochondrial dynamics and mitochondrial QC and discussed potential implications of Parkin inactivation in cancer.

Other ubiquitin ligases implicated in mitochondrial dynamics and deregulated in cancer include, for example, Siah2 or March5. Expression and activity of Siah2 is regulated by stress signals often activated in cancer, such as hypoxia, p38 activity, or responses to ER stress [53]. Siah2 controls mitochondrial fission through its regulation of AKAP121 under stress conditions including hypoxia. In the absence of Siah2 activity, Drp1/Fis1 interaction is impaired and fission is inhibited. The implication of this regulation for physiological conditions under which fission is required, was demonstrated for cardiomyocyte apoptosis, mice survival to myocardial infarction and *C. elegans* life span [5]. A functional link between protein homeostasis and fission exist as Siah2 is transcriptionally regulated by ER stress, namely the UPR machinery (both ATF4 and sXBP1 bind to Siah2 promoter and induces its transcription) [54]. It will be interesting to evaluate whether Siah2 contributes to mitochondrial phenotypes, such as mitochondrial fragmentation or mitochondrial reprogramming in cancer.

Studies on the functional role of the mitochondria-resident E3 ubiquitin ligase March5/Mitol in cancer are missing, although March5 RING-domain mutations are reported in patients with endometrial cancer [55*]. Assessing a potential link between March5 activity and mitochondrial morphology or function is complicated as experimental inactivation of March5 promotes conflicting phenotypes. For example, March5 knockdown [56] or expression of the March5^{H43W}-RING mutant results in elongated, hyperfused mitochondria [55*,57], which antagonizes mitochondrial stress-induced apoptosis [57,58]. By contrast, March5 knockout cells displays fragmented mitochondria [59,60*], and accordingly, are more sensitive to apoptotic insults [60*]. It is feasible that the genetic background, cellular stress level or culture conditions influence March5-activity, and further studies are required to clarify the role of March5 in mitochondrial dynamics.

Additional March5 functions are reported that indirectly affect mitochondrial morphology and may contribute to cancer associated phenotypes. March5 is implicated in mitochondrial QC mechanisms by targeting denatured mitochondrial proteins for degradation (e.g. mutant SOD1 or polyQ proteins), which would otherwise cause mitochondrial damage [59]. As a RING finger ubiquitin ligase, March5 regulates its own protein levels (auto-ubiquitination). Mutations within the RING domain of March5 results in its accumulation, with concomitant mitochondrial stress, which is seen as part of a hyperfused mitochondrial phenotype [55*]. Such stress-induced mitochondrial hyperfusion reportedly occurs in response to stresses that inhibit protein translation [6,26,61], suggesting that accumulation of the March5 mutant induces homeostatic stress response pathways to inhibit mitophagy, increase ATP production, and prevent apoptosis. Interestingly, March5-mediated hyperfusion results in

MAPL-dependent nuclear factor kappa B activation, which contributes to apoptosis resistance by upregulating antiapoptotic proteins [55*,62*].

Mitochondrial Ca^{2+} -overload is a potent proapoptotic signal transferred from the ER to the mitochondria, and several mechanisms are reported that interfere with ER-mitochondria- Ca^{2+} -transfer to increase apoptosis resistance in cancer [63]. March5 mediates non-proteolytic ubiquitination of mitochondrial MFN2, leading to MFN2 oligomerization and increased mitochondrial-ER tethering. March5 knockdown diminishes these contacts and decreases mitochondrial Ca^{2+} uptake [64**]. Thus, it is tempting to speculate that cancer-related March5 mutants contribute to apoptosis resistance.

Concluding remarks

Almost one century ago, Otto Warburg concluded from his studies on aerobic glycolysis of cancer cells, that mitochondria are inactivated in cancer. His research significantly enhanced our understanding of tumor biology, and metabolic reprogramming is considered a hallmark of cancer. Extensive research in the field of cancer metabolism over the last decades, revisited Warburg's initial conclusion and demonstrated that mitochondria are active in cancer cells and utilized for biosynthetic processes, as well as energy production [65]. Major cancer related pathways (e.g. MAPK, PI3K/AKT) reprogram mitochondrial function and dynamics, and cancer cells rely on such reprogramming for sustained proliferation, the capacity to metastasize or to resist apoptosis, thus positioning mitochondria as an important regulatory hub for major cancer traits. Yet, understanding the contribution of the mitochondrial shape to mitochondrial function and cancer-related phenotypes is in its infancy. Recent advances in the field identified an intricate interplay between regulators of mitochondrial QC, dynamics, and apoptosis, which dictates cell fate under stress conditions. Tumor cells are constantly exposed to such stresses, and trigger adaptive responses that in turn, fuel tumor growth, metastasis, and therapy resistance. Additionally, microenvironmental stresses impact intratumoral heterogeneity and impose stem-like traits on cancer cells. The recent finding that mitochondrial morphology is heterogeneous and contributes to a stem-like phenotype in glioblastoma, implies that mitochondrial dynamics are central players in this activity. Based on the implication of mitochondrial dynamics in fundamental cancer-related processes, future research will deepen our understanding of tumor biology. Our better understanding of processes that are engaged in the control of mitochondrial dynamics and their significance for tumor cell development and maintenance, allow the considerations of means to alter mitochondrial dynamics in cancer, thereby offering new possible therapeutic modalities. Ongoing and future studies will define whether such approach is feasible and its impact on cancer, at its different stages.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Von Stockum S, Nardin A, Schrepfer E, Ziviani E. Mitochondrial dynamics and mitophagy in Parkinson's disease: A fly point of view. *Neurobiology of disease*. 2015
2. Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. *Science*. 2012; 337:1062–1065. [PubMed: 22936770]
3. Mitra K, Wunder C, Roysam B, Lin G, Lippincott-Schwartz J. A hyperfused mitochondrial state achieved at G1-S regulates cyclin E buildup and entry into S phase. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:11960–11965. [PubMed: 19617534]
4. Kashatus DF, Lim KH, Brady DC, Pershing NL, Cox AD, Counter CM. RALA and RALBP1 regulate mitochondrial fission at mitosis. *Nature cell biology*. 2011; 13:1108–1115. [PubMed: 21822277]
5. Kim H, Scimia MC, Wilkinson D, Trelles RD, Wood MR, Bowtell D, Dillin A, Mercola M, Ronai ZA. Fine-tuning of Drp1/Fis1 availability by AKAP121/Siah2 regulates mitochondrial adaptation to hypoxia. *Molecular cell*. 2011; 44:532–544. [PubMed: 22099302]
6. Rambold AS, Kostecky B, Elia N, Lippincott-Schwartz J. Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. *Proceedings of the National Academy of Sciences of the United States of America*. 2011; 108:10190–10195. [PubMed: 21646527]
7. Rossignol R, Gilkerson R, Aggeler R, Yamagata K, Remington SJ, Capaldi RA. Energy substrate modulates mitochondrial structure and oxidative capacity in cancer cells. *Cancer research*. 2004; 64:985–993. [PubMed: 14871829]
8. Serasinghe MN, Wieder SY, Renault TT, Elkhali R, Ascioia JJ, Yao JL, Jadoo O, Hoehn K, Kageyama Y, Sesaki H, et al. Mitochondrial division is requisite to RAS-induced transformation and targeted by oncogenic MAPK pathway inhibitors. *Molecular cell*. 2015; 57:521–536. [PubMed: 25658204] The authors demonstrate that ERK-mediated phosphorylation of Drp1 promotes fission which is essential for Ras-mediated transformation and mitochondrial reprogramming. This is the first study to demonstrate that MAPK-inhibition downregulates Drp1, induces fusion and restores mitochondrial function in cancer cells.
9. Senft D, Ronai ZA. UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. *Trends in biochemical sciences*. 2015; 40:141–148. [PubMed: 25656104]
10. Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE, Chan DC. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. *The Journal of cell biology*. 2003; 160:189–200. [PubMed: 12527753]
11. Ishihara N, Nomura M, Jofuku A, Kato H, Suzuki SO, Masuda K, Otera H, Nakanishi Y, Nonaka I, Goto Y, et al. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. *Nature cell biology*. 2009; 11:958–966. [PubMed: 19578372]
12. Wakabayashi J, Zhang Z, Wakabayashi N, Tamura Y, Fukaya M, Kensler TW, Iijima M, Sesaki H. The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice. *The Journal of cell biology*. 2009; 186:805–816. [PubMed: 19752021]
13. Burte F, Carelli V, Chinnery PF, Yu-Wai-Man P. Disturbed mitochondrial dynamics and neurodegenerative disorders. *Nature reviews. Neurology*. 2015; 11:11–24. [PubMed: 25486875]
14. Song M, Dorn GW 2nd. Mitochondria: noncanonical functioning of dynamin factors in static mitochondria of the heart. *Cell metabolism*. 2015; 21:195–205. [PubMed: 25651174]
15. Sugiura A, McLelland GL, Fon EA, McBride HM. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. *The EMBO journal*. 2014; 33:2142–2156. [PubMed: 25107473]
16. Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, Sideris DP, Fogel AI, Youle RJ. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature*. 2015; 524:309–314. [PubMed: 26266977] Demonstrated for the first time that PINK1 phosphorylated ubiquitin

serves as a signal to recruit autophagy receptors to the mitochondria and revealed that PINK1 can trigger mitophagy in the absence of Parkin.

17.
Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, Kimura Y, Tsuchiya H, Yoshihara H, Hirokawa T, et al. Ubiquitin is phosphorylated by PINK1 to activate parkin. *Nature*. 2014; 510:162–166. [PubMed: 24784582] This study links two important signaling pathways by demonstrating that ubiquitin is phosphorylated and show that phosphorylated ubiquitin is a potent activator of Parkin.
18. Chen Y, Dorn GW 2nd. PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. *Science*. 2013; 340:471–475. [PubMed: 23620051]
19. Ziviani E, Tao RN, Whitworth AJ. Drosophila parkin requires PINK1 for mitochondrial translocation and ubiquitinates mitofusin. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:5018–5023. [PubMed: 20194754]
20. McLelland GL, Soubannier V, Chen CX, McBride HM, Fon EA. Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. *The EMBO journal*. 2014; 33:282–295. [PubMed: 24446486]
21. Norris KL, Hao R, Chen LF, Lai CH, Kapur M, Shaughnessy PJ, Chou D, Yan J, Taylor JP, Engelender S, et al. Convergence of Parkin, PINK1, and alpha-Synuclein on Stress-induced Mitochondrial Morphological Remodeling. *The Journal of biological chemistry*. 2015; 290:13862–13874. [PubMed: 25861987]
22.
Hollville E, Carroll RG, Cullen SP, Martin SJ. Bcl-2 family proteins participate in mitochondrial quality control by regulating Parkin/PINK1-dependent mitophagy. *Molecular cell*. 2014; 55:451–466. [PubMed: 24999239] This is the first report that Parkin-interaction with antiapoptotic Bcl-2 proteins limits mitophagy whereas proapoptotic BH3-only proteins enhance mitophagy.
23.
Carroll RG, Hollville E, Martin SJ. Parkin sensitizes toward apoptosis induced by mitochondrial depolarization through promoting degradation of Mcl-1. *Cell reports*. 2014; 9:1538–1553. [PubMed: 25456142] The authors demonstrate a cytotoxic function of Parkin. Upon mitochondrial depolarization, Parkin targets Mcl-1 for degradation, thereby setting a threshold for apoptosis-induction.
24.
Wang Y, Serricchio M, Jauregui M, Shanbhag R, Stoltz T, Di Paolo CT, Kim PK, McQuibban GA. Deubiquitinating enzymes regulate PARK2-mediated mitophagy. *Autophagy*. 2015; 11:595–606. [PubMed: 25915564] Demonstrated that Parkin-mediated ubiquitination of MOM-proteins is counteracted by the de-ubiquitinating enzymes USP30 and USP35 to delay mitophagy.
25.
Liang JR, Martinez A, Lane JD, Mayor U, Clague MJ, Urbe S. USP30 deubiquitylates mitochondrial Parkin substrates and restricts apoptotic cell death. *EMBO reports*. 2015; 16:618–627. [PubMed: 25739811] Revealed that USP30 not only counteracts mitophagy but also Parkin-mediated apoptosis as well as apoptosis induced by BH3-mimetics.
26. Gomes LC, Di Benedetto G, Scorrano L. During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. *Nature cell biology*. 2011; 13:589–598. [PubMed: 21478857]
27. Vance JE. MAM (mitochondria-associated membranes) in mammalian cells: lipids and beyond. *Biochimica et biophysica acta*. 2014; 1841:595–609. [PubMed: 24316057]
28. Morciano G, Giorgi C, Balestra D, Marchi S, Perrone D, Pinotti M, Pinton P. Mcl-1 involvement in mitochondrial dynamics is associated with apoptotic cell death. *Molecular biology of the cell*. 2015

29. Szabadkai G, Simoni AM, Chami M, Wieckowski MR, Youle RJ, Rizzuto R. Drp-1-dependent division of the mitochondrial network blocks intraorganellar Ca²⁺ waves and protects against Ca²⁺-mediated apoptosis. *Molecular cell*. 2004; 16:59–68. [PubMed: 15469822]
30. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, et al. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *The EMBO journal*. 2008; 27:433–446. [PubMed: 18200046]
31. Renault TT, Floros KV, Elkholi R, Corrigan KA, Kushnareva Y, Wieder SY, Lindtner C, Serasinghe MN, Asciolla JJ, Buettner C, et al. Mitochondrial shape governs BAX-induced membrane permeabilization and apoptosis. *Molecular cell*. 2015; 57:69–82. [PubMed: 25482509] This study demonstrates for the first time that fission and fusion processes adapt mitochondrial membrane curvature to allow efficient Bax activation.
32. Prudent J, Zunino R, Sugiura A, Mattie S, Shore GC, McBride HM. MAPL SUMOylation of Drp1 Stabilizes an ER/Mitochondrial Platform Required for Cell Death. *Molecular cell*. 2015; 59:941–955. [PubMed: 26384664] Identified that SUMOylation of Drp1 determines apoptosis kinetics by stabilizing an ER/mitochondrial signaling platform to increase ER-mitochondrial Ca²⁺ transfer, which mediates cristae remodeling and cytochrome c release.
33. Rehman J, Zhang HJ, Toth PT, Zhang Y, Marsboom G, Hong Z, Salgia R, Husain AN, Wietholt C, Archer SL. Inhibition of mitochondrial fission prevents cell cycle progression in lung cancer. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2012; 26:2175–2186. [PubMed: 22321727]
34. Zhao J, Zhang J, Yu M, Xie Y, Huang Y, Wolff DW, Abel PW, Tu Y. Mitochondrial dynamics regulates migration and invasion of breast cancer cells. *Oncogene*. 2013; 32:4814–4824. [PubMed: 23128392] The authors report altered expression of Drp1 and Mfn1 accompanied by a fragmented mitochondrial phenotype in invasive breast cancer cells and lymph node metastasis. They demonstrate that fission promotes mitochondrial trafficking to lamellipodia, thereby increasing migration. Fusion in turn inhibits migration of breast cancer cells.
35. Wan YY, Zhang JF, Yang ZJ, Jiang LP, Wei YF, Lai QN, Wang JB, Xin HB, Han XJ. Involvement of Drp1 in hypoxia-induced migration of human glioblastoma U251 cells. *Oncology reports*. 2014; 32:619–626. [PubMed: 24899388]
36. Hagenbuchner J, Kuznetsov AV, Obexer P, Ausserlechner MJ. BIRC5/Survivin enhances aerobic glycolysis and drug resistance by altered regulation of the mitochondrial fusion/fission machinery. *Oncogene*. 2013; 32:4748–4757. [PubMed: 23146905]
37. Inoue-Yamauchi A, Oda H. Depletion of mitochondrial fission factor DRP1 causes increased apoptosis in human colon cancer cells. *Biochemical and biophysical research communications*. 2012; 421:81–85. [PubMed: 22487795]
38. Kashatus JA, Nascimento A, Myers LJ, Sher A, Byrne FL, Hoehn KL, Counter CM, Kashatus DF. Erk2 phosphorylation of Drp1 promotes mitochondrial fission and MAPK-driven tumor growth. *Molecular cell*. 2015; 57:537–551. [PubMed: 25658205] The authors demonstrate that ERK-mediated phosphorylation of Drp1 promotes fission which is essential for Ras-mediated transformation. They further demonstrate that pancreatic tumor growth in xenograft experiments requires Drp1 activity.
39. Caino MC, Ghosh JC, Chae YC, Vaira V, Rivadeneira DB, Favarsani A, Rampini P, Kossenkova AV, Aird KM, Zhang R, et al. PI3K therapy reprograms mitochondrial trafficking to fuel tumor cell invasion. *Proceedings of the National Academy of Sciences of the United States of America*. 2015;

112:8638–8643. [PubMed: 26124089] This study demonstrates for the first time that PI3K-inhibition induces a migratory response in cancer cells which relies on mitochondrial trafficking and MFN1-dependent fusion.

40. Ni HM, Williams JA, Ding WX. Mitochondrial dynamics and mitochondrial quality control. *Redox biology*. 2015; 4:6–13. [PubMed: 25479550]
41. Gong Y, Zack TI, Morris LG, Lin K, Hukkelhoven E, Raheja R, Tan IL, Turcan S, Veeriah S, Meng S, et al. Pan-cancer genetic analysis identifies PARK2 as a master regulator of G1/S cyclins. *Nature genetics*. 2014; 46:588–594. [PubMed: 24793136]
42. Katajisto P, Dohla J, Chaffer CL, Pentimikko N, Marjanovic N, Iqbal S, Zoncu R, Chen W, Weinberg RA, Sabatini DM. Stem cells. Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness. *Science*. 2015; 348:340–343. [PubMed: 25837514] This study uses an elegant approach to label „old“ mitochondrial proteins and demonstrates that mitochondria are actively sorted during asymmetric stem cell division in an Drp1- and Parkin-dependent manner.
43. Xie Q, Wu Q, Horbinski CM, Flavahan WA, Yang K, Zhou W, Dombrowski SM, Huang Z, Fang X, Shi Y, et al. Mitochondrial control by DRP1 in brain tumor initiating cells. *Nature neuroscience*. 2015; 18:501–510. [PubMed: 25730670] This is the first study to demonstrate a role for Drp1-mediated fission in the maintenance of glioblastoma stem cells, whereas decreased Drp1 activity is associated with differentiated cancer cells.
44. Wang H, Song P, Du L, Tian W, Yue W, Liu M, Li D, Wang B, Zhu Y, Cao C, et al. Parkin ubiquitinates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics in Parkinson disease. *The Journal of biological chemistry*. 2011; 286:11649–11658. [PubMed: 21292769]
45. Che TF, Lin CW, Wu YY, Chen YJ, Han CL, Chang YL, Wu CT, Hsiao TH, Hong TM, Yang PC. Mitochondrial translocation of EGFR regulates mitochondria dynamics and promotes metastasis in NSCLC. *Oncotarget*. 2015; 6:37349–37366. [PubMed: 26497368]
46. Desai SP, Bhatia SN, Toner M, Irimia D. Mitochondrial localization and the persistent migration of epithelial cancer cells. *Biophysical journal*. 2013; 104:2077–2088. [PubMed: 23663851]
47. Ferreira-da-Silva A, Valacca C, Rios E, Populo H, Soares P, Sobrinho-Simoes M, Scorrano L, Maximo V, Campello S. Mitochondrial dynamics protein Drp1 is overexpressed in oncogenic thyroid tumors and regulates cancer cell migration. *PloS one*. 2015; 10:e0122308. [PubMed: 25822260]
48. Zhang B, Wang J, Huang Z, Wei P, Liu Y, Hao J, Zhao L, Zhang F, Tu Y, Wei T. Aberrantly upregulated TRAP1 is required for tumorigenesis of breast cancer. *Oncotarget*. 2015
49. Mujcic H, Hill RP, Koritzinsky M, Wouters BG. Hypoxia signaling and the metastatic phenotype. *Current molecular medicine*. 2014; 14:565–579. [PubMed: 24894165]
50. Han XJ, Yang ZJ, Jiang LP, Wei YF, Liao MF, Qian Y, Li Y, Huang X, Wang JB, Xin HB, et al. Mitochondrial dynamics regulates hypoxia-induced migration and antineoplastic activity of cisplatin in breast cancer cells. *International journal of oncology*. 2015; 46:691–700. [PubMed: 25434519]
51. Escobar-Henriques M, Langer T. Dynamic survey of mitochondria by ubiquitin. *EMBO reports*. 2014; 15:231–243. [PubMed: 24569520]
52. Franz A, Kevei E, Hoppe T. Double-edged alliance: mitochondrial surveillance by the UPS and autophagy. *Current opinion in cell biology*. 2015; 37:18–27. [PubMed: 26343990]
53. Qi J, Ronai ZAA. Dysregulation of ubiquitin ligases in cancer. *Drug Resistance Updates*. 2015; 23:1–11. [PubMed: 26690337]
54. Scortegagna M, Kim H, Li JL, Yao H, Brill LM, Han J, Lau E, Bowtell D, Haddad G, Kaufman RJ, et al. Fine tuning of the UPR by the ubiquitin ligases Siah1/2. *PLoS genetics*. 2014; 10:e1004348. [PubMed: 24809345]
- 55.

- Kim SH, Park YY, Yoo YS, Cho H. Self-clearance mechanism of mitochondrial E3 ligase MARCH5 contributes to mitochondria quality control. *The FEBS journal*. 2015 This is the first study to suggest a role of March5 mutations in cancer. In vitro analysis reveals that March5 RING mutants accumulate in the absence of WT March5 and induce mitochondrial hyperfusion and protect cells from apoptosis.
56. Park YY, Lee S, Karbowski M, Neutzner A, Youle RJ, Cho H. Loss of MARCH5 mitochondrial E3 ubiquitin ligase induces cellular senescence through dynamin-related protein 1 and mitofusin 1. *Journal of cell science*. 2010; 123:619–626. [PubMed: 20103533]
57. Fang L, Hemion C, Goldblum D, Meyer P, Orgul S, Frank S, Flammer J, Neutzner A. Inactivation of MARCH5 prevents mitochondrial fragmentation and interferes with cell death in a neuronal cell model. *PloS one*. 2012; 7:e52637. [PubMed: 23285122]
58. Park YY, Nguyen OT, Kang H, Cho H. MARCH5-mediated quality control on acetylated Mfn1 facilitates mitochondrial homeostasis and cell survival. *Cell death & disease*. 2014; 5:e1172. [PubMed: 24722297]
59. Nagashima S, Tokuyama T, Yonashiro R, Inatome R, Yanagi S. Roles of mitochondrial ubiquitin ligase MITOL/MARCH5 in mitochondrial dynamics and diseases. *Journal of biochemistry*. 2014; 155:273–279. [PubMed: 24616159]
- 60.
- Xu S, Cherok E, Das S, Li S, Roelofs BA, Ge SX, Polster BM, Boyman L, Lederer WJ, Wang C, et al. Mitochondrial E3 ubiquitin ligase MARCH5 controls mitochondrial fission and cell sensitivity to stress-induced apoptosis through regulation of MiD49 protein. *Molecular biology of the cell*. 2015 This study identifies the mitochondrial Drp1-adaptor protein Mid49, but not Drp1 or Mfn1, as a substrate for March5 in March5 knockout cells and demonstrates that March5-mediated Mid49 degradation restricts excessive fusion and apoptosis.
61. Tondera D, Grandemange S, Jourdain A, Karbowski M, Mattenberger Y, Herzig S, Da Cruz S, Clerc P, Raschke I, Merkwirth C, et al. SLP-2 is required for stress-induced mitochondrial hyperfusion. *The EMBO journal*. 2009; 28:1589–1600. [PubMed: 19360003]
- 62.
- Zemirli N, Pourcelot M, Ambroise G, Hatchi E, Vazquez A, Arnoult D. Mitochondrial hyperfusion promotes NF-kappaB activation via the mitochondrial E3 ligase MULAN. *The FEBS journal*. 2014; 281:3095–3112. [PubMed: 24841215] The authors reveal that mitochondrial hyperfusion leads to MAPL-dependent NF-kappaB activation which contributes to apoptosis resistance via upregulation of antiapoptotic proteins.
63. van Vliet AR, Verfaillie T, Agostinis P. New functions of mitochondria associated membranes in cellular signaling. *Biochimica et biophysica acta*. 2014; 1843:2253–2262. [PubMed: 24642268]
- 64.
- Sugiura A, Nagashima S, Tokuyama T, Amo T, Matsuki Y, Ishido S, Kudo Y, McBride HM, Fukuda T, Matsushita N, et al. MITOL regulates endoplasmic reticulum-mitochondria contacts via Mitofusin2. *Molecular cell*. 2013; 51:20–34. [PubMed: 23727017] This is the first study to demonstrate that MFN2 is activated by ubiquitination. K63-linked ubiquitination of mitochondrial MFN2 does not affect fusion but increases ER-mitochondria tethering and calcium transfer.
65. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. *Cancer cell*. 2012; 21:297–308. [PubMed: 22439925]
66. Taguchi N, Ishihara N, Jofuku A, Oka T, Mihara K. Mitotic phosphorylation of dynamin-related GTPase Drp1 participates in mitochondrial fission. *The Journal of biological chemistry*. 2007; 282:11521–11529. [PubMed: 17301055]
67. Qi X, Disatnik MH, Shen N, Sobel RA, Mochly-Rosen D. Aberrant mitochondrial fission in neurons induced by protein kinase C{delta} under oxidative stress conditions in vivo. *Molecular biology of the cell*. 2011; 22:256–265. [PubMed: 21119009]

68. Cribbs JT, Strack S. Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death. *EMBO reports*. 2007; 8:939–944. [PubMed: 17721437]
69. Han XJ, Lu YF, Li SA, Kaitsuka T, Sato Y, Tomizawa K, Nairn AC, Takei K, Matsui H, Matsushita M. CaM kinase I alpha-induced phosphorylation of Drp1 regulates mitochondrial morphology. *The Journal of cell biology*. 2008; 182:573–585. [PubMed: 18695047]
70. Wang W, Wang Y, Long J, Wang J, Haudek SB, Overbeek P, Chang BH, Schumacker PT, Danesh FR. Mitochondrial fission triggered by hyperglycemia is mediated by ROCK1 activation in podocytes and endothelial cells. *Cell metabolism*. 2012; 15:186–200. [PubMed: 22326220]
71. Bossy B, Petrilli A, Klinglmayr E, Chen J, Lutz-Meindl U, Knott AB, Masliah E, Schwarzenbacher R, Bossy-Wetzel E. S-Nitrosylation of DRP1 does not affect enzymatic activity and is not specific to Alzheimer's disease. *Journal of Alzheimer's disease : JAD*. 2010; 20(Suppl 2):S513–S526. [PubMed: 20463395]
72. Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z, Lipton SA. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science*. 2009; 324:102–105. [PubMed: 19342591]
73. Gawlowski T, Suarez J, Scott B, Torres-Gonzalez M, Wang H, Schwappacher R, Han X, Yates JR 3rd, Hoshijima M, Dillmann W. Modulation of dynamin-related protein 1 (DRP1) function by increased O-linked-beta-N-acetylglucosamine modification (O-GlcNAc) in cardiac myocytes. *The Journal of biological chemistry*. 2012; 287:30024–30034. [PubMed: 22745122]
74. Zunino R, Braschi E, Xu L, McBride HM. Translocation of SenP5 from the nucleoli to the mitochondria modulates DRP1-dependent fission during mitosis. *The Journal of biological chemistry*. 2009; 284:17783–17795. [PubMed: 19411255]
75. Zunino R, Schauss A, Rippstein P, Andrade-Navarro M, McBride HM. The SUMO protease SENP5 is required to maintain mitochondrial morphology and function. *Journal of cell science*. 2007; 120:1178–1188. [PubMed: 17341580]
76. Guo C, Hildick KL, Luo J, Dearden L, Wilkinson KA, Henley JM. SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemia. *The EMBO journal*. 2013; 32:1514–1528. [PubMed: 23524851]
77. Horn SR, Thomenius MJ, Johnson ES, Freel CD, Wu JQ, Coloff JL, Yang CS, Tang W, An J, Ilkayeva OR, et al. Regulation of mitochondrial morphology by APC/CCdh1-mediated control of Drp1 stability. *Molecular biology of the cell*. 2011; 22:1207–1216. [PubMed: 21325626]
78. Pyakurel A, Savoia C, Hess D, Scorrano L. Extracellular regulated kinase phosphorylates mitofusin 1 to control mitochondrial morphology and apoptosis. *Molecular cell*. 2015; 58:244–254. [PubMed: 25801171]
79. Lee JY, Kapur M, Li M, Choi MC, Choi S, Kim HJ, Kim I, Lee E, Taylor JP, Yao TP. MFN1 deacetylation activates adaptive mitochondrial fusion and protects metabolically challenged mitochondria. *Journal of cell science*. 2014; 127:4954–4963. [PubMed: 25271058] This study demonstrates that HDAC-dependent deacetylation of MFN1 activates fusion and diminishes ROS production under glucose starvation in vitro and in fasting mice.
80. Leboucher GP, Tsai YC, Yang M, Shaw KC, Zhou M, Veenstra TD, Glickman MH, Weissman AM. Stress-induced phosphorylation and proteasomal degradation of mitofusin 2 facilitates mitochondrial fragmentation and apoptosis. *Molecular cell*. 2012; 47:547–557. [PubMed: 22748923]
81. Senyilmaz D, Virtue S, Xu X, Tan CY, Griffin JL, Miller AK, Vidal-Puig A, Teleanu AA. Regulation of mitochondrial morphology and function by stearylolation of TFR1. *Nature*. 2015; 525:124–128. [PubMed: 26214738] This is the first study to describe a dietary regulation of mitochondrial function. Dietary uptake of stearic acid determines stearylolation-level of TFR1 and lack of this metabolic mark on TRF1 promotes JNK-mediated activation of Huwe1, ubiquitination and

degradation of MFN and mitochondrial damage, which can be reverted by dietary supplementation with stearic acid.

82. Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH, Taanman JW. Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. *Human molecular genetics*. 2010; 19:4861–4870. [PubMed: 20871098]
83. Glauser L, Sonnay S, Stafa K, Moore DJ. Parkin promotes the ubiquitination and degradation of the mitochondrial fusion factor mitofusin 1. *Journal of neurochemistry*. 2011; 118:636–645. [PubMed: 21615408]
84. Anton F, Dittmar G, Langer T, Escobar-Henriques M. Two deubiquitylases act on mitofusin and regulate mitochondrial fusion along independent pathways. *Molecular cell*. 2013; 49:487–498. [PubMed: 23317502]

Highlights

- The interplay of regulators of mitophagy, mitochondrial dynamics, and apoptosis controls cell fate
- Mitochondrial dynamics impacts transformation, stemness, and cancer cell migration
- Ubiquitin ligases deregulated in cancer control mitochondrial morphology

Figure 1. Mitochondrial Dynamics

The double membrane structure of the mitochondrion creates distinct compartments. The mitochondrial outer membrane (MOM) and the mitochondrial inner membrane (MIM) separate the intermembrane space (IMS) from the cytoplasm and the mitochondrial matrix. The electron transport machinery is located in invaginations of the MIM, called cristae. Mitochondrial morphology is determined by a balance between fusion and fission events, mediated by dynamin related GTPases (Drp1, MFN1/2, OPA1). Increased fission events or decreased fusion events results in a fragmented mitochondrial network as observed during mitosis or upon severe stress (e.g. hypoxia, apoptotic insults). Increased fission is necessary to equally distribute mitochondria among daughter cells, and mitochondrial trafficking within the cell. It facilitates mitophagy and is associated with apoptosis. When fusion exceeds fission, elongated mitochondria, often highly interconnected, display increased oxidative capacity, and increased contacts with the endoplasmic reticulum (ER). Increased fusion is observed following nutrient starvation or mild stresses and is considered a homeostatic event to dilute damaged mitochondrial molecules (oxidized lipids, proteins, DNA), escape autophagy and prevent cell death, although fusion reportedly enhances cell death in response to certain stimuli.

Figure 2. Mitochondrial dynamics, quality control and cell fate decision

Dependent on the type and severity of stress, mitochondria undergo either fusion or fission to activate homeostatic pathways or precede cell death. Hyperfused mitochondria relieve mitochondrial stress by complementation of damaged content. They resist mitophagy and increase ATP production to adjust to cellular stresses as nutrient deprivation. ER-mitochondrial Ca^{2+} -transfer increased mitochondrial function, while extensive Ca^{2+} -overload results in cell death programs. Asymmetric fission segregates mitochondrial content in a polarized manner, resulting in one hyperpolarized mitochondria that is removed from the network by mitophagy, and one hypopolarized, which is reintroduced into the healthy mitochondrial pool. Assymmetric fission relies on Drp-1 activity, but the underlying mechanism of polarized segregation of mitochondrial content remains to be determined. Pink1/Parkin-mediated mitophagy is under posttranslational control (proteolytic cleavage, phosphorylation and ubiquitination) and can be counteracted by de-ubiquitinating enzymes or protein-protein interaction between Parkin and antiapoptotic Bcl-2 proteins. Increased Parkin-activity is associated with a shift towards a pro-apoptotic response, as excessive proteasomal degradation of MOM proteins result in mitochondrial membrane disruption and cytochrome c leakage. Parkin-mediated ubiquitination and subsequent degradation of antiapoptotic Mcl-1 increases Bax/Bak-dependent membrane permeabilization and triggers apoptosis.

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**]
	PKC δ	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]
	CAMK1	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; coincides 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*]
MFN2	March5	Ubi	Degradation	Targets acetylated Mfn1 more efficiently; prevents Mfn1 accumulation and cell death under mitochondrial stress conditions.	[58]
	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**]

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Substrate	Regulator	Signal	Effect	Comment	Refs
	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;