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News & Views

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Mitochondria just wanna have FUN(DC1)

Alexander M van der Bliek

A fascinating story is unfolding at the interface between mitochondria and the ER. Two new papers, one in this issue of *The EMBO Journal* (Wu *et al*, 2016) and one in the journal *Autophagy* (Chen *et al*, 2016), further clarify the role of mitochondrial outer membrane protein FUNDC1 in autophagy and connect it to mitochondrial fission occurring at the interface between mitochondria and the ER.

See also: **W Wu *et al*** (July 2016)

Several years ago, the laboratory of Quan Chen discovered a new mitochondrial outer membrane protein required for mitophagy when it is induced by hypoxia (Liu *et al*, 2012). This protein, called FUNDC1 (Fun14 domain containing protein 1), is anchored in the mitochondrial outer membrane by three predicted transmembrane segments. The cytosolic N-terminal domain of FUNDC1 has a LIR (an LC3 interacting region) that helps recruit autophagic isolation membrane to mitochondria under hypoxic conditions. Whether and how FUNDC1 would be concomitantly linked to mitochondrial dynamics such as fission and fusion remained unclear. New work now shows that FUNDC1 exerts its function at the interface between mitochondria and the ER and thereby controls mitochondrial dynamics and mitophagy.

The interface between mitochondria and the ER, which is commonly referred to as the MAM (mitochondrion associated membrane), performs a plethora of functions (Phillips & Voeltz, 2016). The MAM brings together key signaling pathways that help decide between apoptosis and autophagy in response to cellular stress. It is furthermore involved in calcium transfer between the organelles through close coupling of uptake and release channels. The MAM also facilitates the transfer of lipids between the organelles through specialized lipid transfer proteins. More relevant for this discussion are the roles of the MAM in mitochondrial fission, apoptosis, and mitophagy. These three processes are—figuratively speaking—joined at the hip in the MAM. Many mitochondrial fission, apoptosis, and autophagy proteins localize to the MAM where they can influence each others' activities while utilizing the close contact between the two organelles. Mitochondrial fission, for example, can start with an ER protein, INF2, driving constriction of the mitochondrion through actin assembly at the MAM. This initial constriction is helpful, because the diameters of rings made by the canonical mitochondrial fission protein Drp1 are much smaller than the diameter of a typical mitochondrion.

Apoptosis and autophagy cross paths in the MAM as well. Bcl-2, which is a key anti-apoptotic protein, binds to the autophagy protein beclin-1 on the ER membrane (Mukhopadhyay *et al*, 2014). Modification of one or the other of these two proteins can help decide between apoptosis and autophagy, while mitochondrial fission at the MAM promotes BAX-pore formation and cytochrome c release during apoptosis. The MAM thus serves as a site for initiating autophagosome formation and it is the site for acting on apoptotic triggers. This complicated dance of apoptosis, autophagy, and mitochondrial fission proteins shows that the MAM plays a critical role in decisions concerning cell growth and survival.

Two new studies now bring FUNDC1 into this mix. The Feng/Li/Zhang laboratories showed that inducing hypoxia causes a shift in FUNDC1 binding partners (Wu *et al*, 2016). FUNDC1 relocates to the MAM where it first binds to calnexin, an ER protein that helps form connections between ER and mitochondria (Fig 1). Next, FUNDC1 binds to Drp1, which then leads to mitochondrial fission and ultimately to mitophagy. These data nicely dovetail data from the Chen/Liu laboratories, which shows that FUNDC1 normally binds to Opa1, a mitochondrial fusion protein in the inter-membrane space, but releases Opa1 when hypoxia is induced (Chen *et al*, 2016). FUNDC1 then binds to Drp1, promoting mitochondrial fission. Together, these data show that FUNDC1 helps coordinate mitochondrial fission at the MAM with hypoxia-induced mitophagy.

Earlier studies from the same laboratories uncovered regulatory pathways that control FUNDC1 during hypoxic mitophagy. Long-term regulation of FUNDC1 is achieved by altering expression levels through the microRNA mir137 (Li *et al*, 2014). This microRNA is down-regulated during hypoxia, thus increasing FUNDC1 expression. Short-term regulation of FUNDC1 is mediated by protein phosphorylation. FUNDC1 can be inactivated by CK2-mediated phosphorylation of Ser13, but is then reactivated by PGAM5-mediated dephosphorylation (Chen *et al*, 2014). The protein phosphatase PGAM5 is itself activated by loss of mitochondrial membrane potential, perhaps acting in parallel with the Pink1 kinase, which also triggers mitophagy in response to loss of membrane potential. Phosphorylation of FUNDC1 by ULK1 kinase adds another layer of regulation (Wu *et al*, 2014). ULK1 is a key regulator of general autophagy. It activates FUNDC1 by phosphorylation at Ser17. FUNDC1 thus responds to a general trigger for autophagy through ULK1 and to a selective trigger for mitophagy through PGAM5.

How does FUNDC1 affect mitophagy? The protein has a LIR, which is a short sequence motif that can bind to LC3 and related members of the GABARAP family on the autophagic isolation membrane (Liu *et al*, 2012). Binding interactions between LC3 and FUNDC1 are strengthened when

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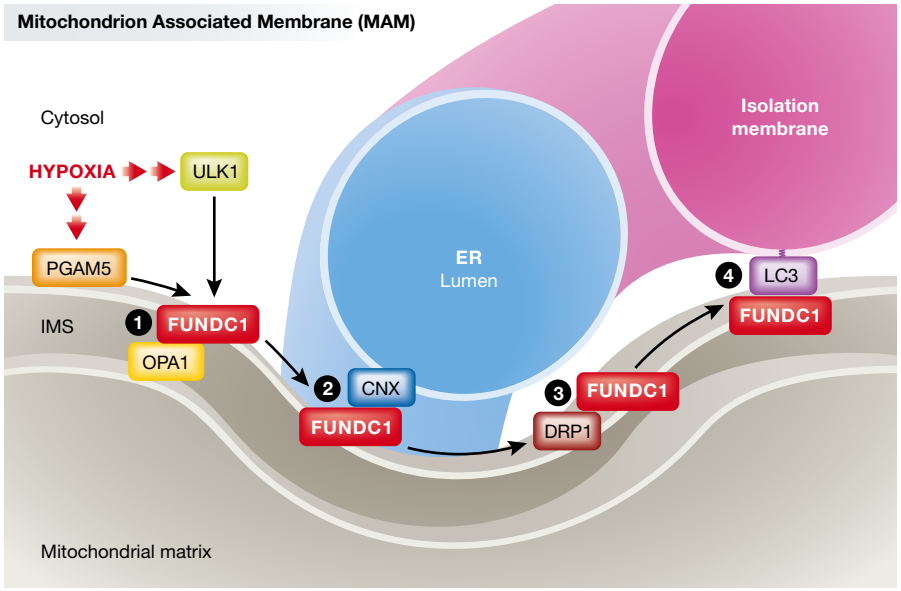

Figure 1. Steps in the FUNDC1 pathway discovered with four different binding interactions.
FUNDC1 first binds to OPA1 (step 1). Phosphorylation at Ser17 by ULK1 and dephosphorylation at Ser13 by PGAM5 activate FUNDC1. After releasing OPA1, FUNDC1 binds to the ER protein calnexin (CNX) in the MAM (step 2), followed by binding to DRP1 and triggering of mitochondrial fission (step 3). Finally, FUNDC1 binds to LC3 on the isolation membrane (step 4), thereby aiding sequestration of the defective mitochondrion in an autophagosome.

Ser13 is dephosphorylated after mitochondria lose their membrane potential. Binding of LC3 to FUNDC1 helps encapsulate the defective mitochondrion with isolation membrane, thus preparing it for degradation in autophagolysosomes. The dephosphorylation of Ser13 by PGAM5 may also occur alongside phosphorylation of Ser17 by the ULK1 kinase. ULK1 is controlled by AMPK, which senses reduced levels of ATP under hypoxic conditions. ULK1 also activates the general autophagy machineries that are needed to make autophagic isolation membrane and to target autophagosomes for fusion with lysosomes.

LIR motifs have been found in NIX and BNIP3, which are two other mitochondrial outer membrane proteins that promote mitophagy (Wei *et al*, 2015). Both proteins can promote mitophagy during hypoxia, just like FUNDC1. There are, however, differences in the ancillary functions of these proteins. NIX, for example, serves to remove mitochondria as part of developmental programs, such as wholesale elimination of mitochondria during erythrocyte maturation. Moreover, BNIP3 and NIX have BH3 domains, which allow them to interact with apoptosis regulators like Bcl-2, while FUNDC1 binds to mitochondrial fission and fusion proteins. Despite these differences, FUNDC1, BNIP3, and NIX can still be classified as receptors for LC3 and GABARAP family members, thus directly promoting receptor-mediated mitophagy.

Receptor-mediated mitophagy contrasts with ubiquitin-dependent mitophagy (Wei *et al*, 2015). The best-known ubiquitin-dependent pathway is mediated by Pink1 and Parkin, but other ubiquitin ligases, such as Mul1, have also been shown to promote mitophagy. These pathways all rely on ubiquitin-binding proteins, such as P62 and optineurin, to bridge the gap between ubiquitin on mitochondrial outer membrane proteins and LC3 or other GABARAP family members on the autophagic isolation membrane. There is overlap between conditions that induce the different pathways for mitophagy. Mutations also show partial redundancy between some pathways. Why then are there so many ways to facilitate mitophagy? Some mechanisms could be more effective in specific cell types or under special circumstances. Redundancy could also provide a much needed backup for this important function.

Binding of FUNDC1 to DRP1 also adds complexity to the mitochondrial fission machinery. DRP1 was previously shown to interact with several other receptors on the surface of mitochondria. These include MFF, FIS1, MID49, and MID51 (Osellame *et al*, 2016). FUNDC1 can now be added to this small gang of mitochondrial fission regulators. The challenge for future investigations will be to sort out how all these different proteins come together in the MAM and then decide which route to pursue: apoptosis, mitophagy, or growth through uneventful homeostatic fission.

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