Text by Ben Short
bshort@rockefeller.edu

Mitochondrial proteases strike the right balance

Two studies reveal how proteases combine to regulate mitochondrial fusion.

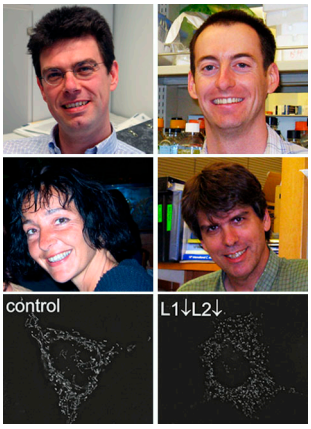
Mitochondria constantly merge and divide to share components and alter their cellular distribution. Maintaining the correct balance between fission and fusion is so important that at least three proteases converge to regulate a key fusion protein, as studies from Ehses et al. and Head et al. now show (1, 2).

Fusion between mitochondria is mediated by GTPases related to the endocytic protein dynamin. Inner membrane fusion is controlled by the OPA1 GTPase, which exists as a carefully attuned mixture of long and short isoforms that are both required for membrane fusion (3, 4). The balance between OPA1 versions is maintained in part by a protease called YME1L, which cleaves long OPA1 to generate the shorter form (3, 5). But the situation is complicated by the existence of OPA1 splice variants that can't be cleaved by YME1L, and by the fact that stress induces the complete cleavage of all long OPA1 so that fusion is blocked and cells can separate damaged mitochondria from their healthier kin (5).

This suggests that OPA1 may be cleaved by other proteases too. The multi-subunit *m*-AAA protease has been implicated (6), but the loss of one of its subunits, paraplegin, doesn't affect mitochondrial dynamics. Thomas Langer, from the University of Cologne, Germany, decided to investigate the role of two homologous subunits, AFG3L1 and AFG3L2, which can form a functional *m*-AAA protease without paraplegin (1).

> "This would be a quick way to stop damaged mitochondria from poisoning the system."

Knocking down either protein alone had no effect on fibroblasts, but depleting both at the same time caused the mitochondrial network to fragment due to a block in organelle fusion. Accordingly, the balance of long and short OPA1 was disrupted in cells lacking AFG3L1 and AFG3L2, although not in the way one might expect.



Focal Point

Two groups of researchers implicate different mitochondrial proteases in the regulation of OPA1, a dynamin-related GTPase that promotes mitochondrial inner membrane fusion. Ehses et al., led by Thomas Langer (top left), find that the *m*-AAA protease maintains the correct balance of long and short OPA1 isoforms—the mitochondrial network is fragmented in the absence of two of the protease's subunits (bottom row). Both groups reveal that a second protease, OMA1, completely cleaves long versions of OPA1 to prevent damaged mitochondria from fusing. Brian Head (top right), Lorena Griparic (center left), Alexander van der Bliek (center right), and colleagues find that OMA1 itself is also regulated by proteolysis.

Rather than accumulating, levels of long OPA1 actually decreased in the absence of the *m*-AAA protease subunits. Long OPA1 was also destabilized in the brain, heart, and kidney of mice lacking AFG3L2.

"This really puzzled us for a long time," admits Langer. "But it turns out that there's another mitochondrial protease that takes over [in the absence of the *m*-AAA protease]." Activation of this additional enzyme—called OMA1—leads to the unregulated degradation of all long OPA1, blocking fusion and fragmenting the mitochondrial network.

Meanwhile, a second team led by Alexander van der Bliek from UCLA had also discovered that OMA1 cleaves OPA1. van der Bliek's group had been searching for the protease that cuts up the fusion protein to prevent dysfunctional mitochondria from sharing their damaged proteins with healthier neighbors. Like Langer's team, they found that knocking down OMA1 prevented OPA1 from being cleaved in response to a loss of mitochondrial membrane potential or depletion of ATP (2). "While YME1L cleaves OPA1 to regulate the balance of short and long forms, OMA1 gets rid of long OPA1 to block fusion," says van der Bliek. Langer agrees, adding that the *m*-AAA protease is also involved in maintaining the constitutive balance of OPA1 isoforms.

Regulating mitochondrial dynamics is clearly critical to a cell's health, particularly within the nervous system. Mutations in OPA1 cause dominant optic atrophy, while the outer membrane fusion protein MFN2 is linked to Charcot-Marie-Tooth disease. The *m*-AAA protease can now be added to the list, because mutations in AFG3L2 cause spinocerebellar ataxia.

The next big question is how OMA1 senses mitochondrial dysfunction—be it loss of membrane potential, ATP depletion, or absence of the *m*-AAA protease. Head et al. suggest that proteolysis of OMA1 itself may be key because a longer, presumably active, form of the protease accumulates upon mitochondrial damage (2). Under normal conditions, this version of OMA1 would be rapidly turned over. "That might seem wasteful," says van der Bliek. "But this would be a quick way to shut fusion down and stop damaged mitochondria from poisoning the system."

1. Ehses, S. et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200906084.
2. Head, B. et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200906083.
3. Song, Z., et al. 2007. *J. Cell Biol.* 178:749–755.
4. Devay, R.M., et al. 2009. *J. Cell Biol.* 186:793–803.
5. Griparic, L., et al. 2007. *J. Cell Biol.* 178:757–764.
6. Ishihara, N., et al. 2006. *EMBO J.* 25:2966–2977.