AUTOPHAGY

TFEB perfects multitasking

“
a link between
autophagy
and lysosomal
biogenesis.
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A new transcription-dependent mechanism regulating autophagy has been identified by a recent study. Ballabio and colleagues reveal that the transcription factor TFEB, which is known to control lysosomal biogenesis, also regulates autophagy.

Autophagy is activated in conditions of starvation by mammalian target of rapamycin complex 1 (mTORC1). However, inhibiting mTORC1 with rapamycin does not induce the transcription of autophagy genes, indicating that an additional pathway may be required. Because lysosomes are integral at later stages of the autophagic pathway, the authors examined whether TFEB has a role in autophagy. Indeed, TFEB overexpression in HeLa cells increased the number of autophagosomes, as measured by the expression of the autophagosome marker LC3 (also known as MAP1LC3), and depletion of TFEB resulted in decreased levels of LC3II (which is generated by conversion of LC3 during autophagy).

Furthermore, cells overexpressing TFEB had more autophagolysosomes (which are formed by the fusion of autophagosomes and lysosomes) than control cells. Thus, it seems that TFEB has a key role in different stages of the autophagy pathway.

Because TFEB is a transcription factor, it probably regulates autophagy by controlling gene expression. The authors confirmed this by showing that cells overexpressing TFEB show increased expression of autophagy genes, similarly to what occurs under starvation conditions. To achieve this, TFEB, which normally resides in the cytoplasm, must translocate to the nucleus, and the authors show that this relocation is triggered by low nutrient levels. But what is the mechanism? By supplementing starvation media with different factors, the authors found that inhibition of mitogen-activated protein kinase (MAPK) signalling stimulates the nuclear translocation of TFEB. Specifically, they show that, under normal

nutrient conditions, the MAPK extracellular signal-regulated kinase (ERK) phosphorylates TFEB at Ser142, which retains TFEB in the cytoplasm. By contrast, under starvation conditions, TFEB is not phosphorylated and can translocate to the nucleus. In support of this, in HeLa cells carrying an unphosphorylatable Ser142Ala TFEB mutant, TFEB showed increased nuclear localization, TFEB target gene expression and autophagolysosome formation. TFEB translocation to the nucleus was also observed following depletion of ERK.

Finally, the authors confirmed their findings *in vivo*. They observed that mice which had been starved for 16 hours showed increased levels of TFEB in the nucleus, enhanced transcription of TFEB target genes (both those associated with autophagy and those involved in lysosomal biogenesis) and decreased levels of ERK-mediated TFEB phosphorylation, compared with fed animals. Furthermore, conditional expression of TFEB led to a significant increase in the number of autophagosomes compared with controls.

Taken together, these findings reveal a new pathway of autophagy regulation and identify, for the first time, a link between autophagy and lysosomal biogenesis.

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ORIGINAL RESEARCH PAPER Settembre, C. et al. TFEB links autophagy to lysosomal biogenesis. *Science* 26 May 2011 (doi:10.1126/science.1204592)

FURTHER READING Sardiello, M. et al. A gene network regulating lysosomal biogenesis and function. *Science* 325, 473–477 (2009) | Klionsky, D. J. Autophagy: from phenomenology to molecular understanding in less than a decade. *Nature Rev. Mol. Cell Biol.* 8, 931–937 (2007)