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CELL SIGNALLING

A peroxisomal home for TSC

> TSC-mediated mTORC1 inhibition in response to ROS production triggers autophagy

Peroxisomes carry out key metabolic functions, and new roles for these mysterious organelles continue to emerge. A peroxisome-based pathway has now been found that blocks signalling from mammalian target of rapamycin complex 1 (mTORC1) and promotes autophagy in response to reactive oxygen species (ROS).

mTORC1 is integral for coordinating environmental conditions with cell growth, and its inhibition under challenging conditions leads to autophagy. This is mediated by tuberous sclerosis complex (TSC), which converts the GTPase RHEB (RAS homologue enriched in brain) into its GDP-bound form, thus blocking its interaction with mTORC1 and inhibiting mTORC1 activation. Previous work had shown that TSC inhibits mTORC1 in response to ROS, but where this occurs had remained unclear.

Walker and colleagues reasoned that, as a major source of ROS, peroxisomes are likely candidates for this. Indeed, they observed that TSC1, TSC2 and RHEB colocalize with the peroxisome marker PMP70, and this localization at peroxisomes was confirmed by cell fractionation analysis. Moreover, they showed that TSC2 resides at the cytosolic surface of the peroxisomal membrane.

Notably, TSC2 co-immunoprecipitated with the peroxisome protein PEX5, which recognizes peroxisome targeting signals (PTS) on proteins and imports them into peroxisomes. Further analysis revealed that TSC2 contains a region homologous to known PTS, mutation of which impaired TSC2 localization to peroxisomes. Similarly, TSC1, which is thought to tether TSC2 to membranes, interacted (through a stretch on its amino-terminal domain) with the peroxisome protein PEX19, which localizes proteins to peroxisomal membranes. One possibility the authors propose is that when TSC2 is transported to peroxisomes by PEX5, it is captured by TSC1 and anchored to the cytosolic face of the peroxisomal membrane.

As TSC normally functions to suppress mTORC1 signalling, Walker and colleagues asked whether this is also the case in peroxisomes. They observed that inhibition of TSC2 localization to these organelles (through mutations that block the TSC2–PEX5 interaction) increased mTORC1 signalling, and this was due to compromised GTPase-activating protein (GAP) activity towards RHEB. Importantly, the GAP activity of mutant TSC2 was intact, as shown by *in vitro* assays, suggesting that the mTORC1 suppression defect is due to abrogated peroxisomal localization rather than loss of GAP activity.

Finally, the authors confirmed that TSC-mediated mTORC1 inhibition in response to ROS production triggers autophagy. Overexpression of TSC1 and TSC2 increased autophagosome formation, and addition of exogenous ROS to cells, or treating cells with drugs that promote ROS production by peroxisomes, promoted mTORC1 suppression and autophagy induction. Furthermore, cells from patients with peroxisome biogenesis disorders were resistant to mTORC1 inhibition following treatment with ROS.

So, this study identifies peroxisomes as the organelles where TSC represses mTORC1 and induces autophagy in response to oxidative stress. Further work is now needed to determine the protein that signals to TSC in response to ROS, and the authors propose that ataxia-telangiectasia mutated (ATM; which localizes to peroxisomes and is activated by ROS) might be a good candidate.

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ORIGINAL RESEARCH PAPER Zhang, J. *et al.* A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS. *Nature Cell Biol.* http://dx.doi.org/10.1038/ncb2822 (2013)