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Connections, connections, connections

Membrane-bound organelles can communicate using vesicular transport, but also by forming direct membrane contact sites (MCSs) where the two membranes are closely apposed (less than 30 nm apart). Recent studies suggest that most, if not all, cell membranes engage in these close contacts, but the molecular composition of different MCSs and their functional significance, particularly in vertebrate systems, remain poorly understood. Three independent studies shed light on the structure and roles of MCSs in human cells.

Gomez-Suaga *et al.* studied the functions of endoplasmic reticulum (ER)–mitochondria MCSs, known as mitochondria-associated ER membranes (MAMs). Membrane tethering at MAMs was previously shown to be mediated by the interaction between VAMP-associated protein B/C (VAPB) on the ER membrane and protein tyrosine phosphatase interacting protein 51 (PTPIP51; also known as RMDN3) on the outer mitochondrial membrane. Reducing the expression of VAPB or PTPIP51 promoted basal autophagy, a process whereby defective or superfluous cellular components are targeted for degradation and recycling. In contrast, overexpression of VAPB and PTPIP51, which promoted MAMs, impaired basal and chemically-induced autophagy. Interestingly, starvation-induced autophagy was not affected, most likely owing to the different mechanisms that govern the various autophagy pathways. Similar observations were made when MAMs were induced by expressing an artificial protein tether, indicating that MAMs are important inhibitors of autophagy. One of the known functions of MAMs is to deliver calcium (Ca^{2+}) to mitochondria, and interfering with Ca^{2+} uptake by mitochondria stimulates autophagy. This led the authors to investigate whether Ca^{2+} exchange at MAMs is important for the inhibition of autophagy. Indeed, VAPB or PTPIP51 overexpression increased ER–mitochondrial Ca^{2+} exchange, and when this exchange was perturbed, autophagic fluxes in VAPB- or PTPIP51-overexpressing cells returned to control levels.

Costello *et al.* and Hua *et al.* studied ER–peroxisome MCSs, and demonstrated independently that VAPB (and its homologue VAPA) and the peroxisomal protein acyl-CoA-binding domain-containing protein 5 (ACBD5) interact at these MCSs. Costello *et al.* showed that overexpression of VAPB and ACBD5 promoted the formation of ER–peroxisome contacts (increasing the proportion of peroxisomes in contact with the ER as well as the interorganellar contact area), whereas these effects were reversed when the proteins were depleted. In both studies, depletion of VAPs or ACBD5 increased peroxisome mobility, indicating that VAP–ACBD5 interactions at MCSs tether ER and peroxisomal membranes. VAP and ACBD5 expression - and hence formation of ER–peroxisome MCSs - was shown to be important for bidirectional lipid exchange between peroxisomes and the ER. Both studies found that peroxisome membrane expansion, which depends on the delivery of lipids from the ER, was consistently perturbed following VAP or ACBD5 depletion; Hua *et al.* also revealed that VAP or ACBD5 deficiency lowers the cellular levels of cholesterol and plasmalogens, the synthesis of which is initiated at peroxisomes and continues in the ER.

Research on MCSs is currently very active and these studies provide new insights into their roles in regulating organelle dynamics and in maintaining organelle and cell homeostasis.

Paulina Strzyz

> “most, if not all, cell membranes engage in these close contacts”

ORIGINAL ARTICLES Gomez-Suaga, P. *et al.* The ER-mitochondria tethering complex VAPB-PTPIP51 regulates autophagy. *Curr. Biol.* **27**, 371–385 (2017) | Costello, J. L. *et al.* ACBD5 and VAPB mediate membrane associations between peroxisomes and the ER. *J. Cell Biol.* **216**, 331–342 (2017) | Hua, R. *et al.* VAPs and ACBD5 tether peroxisomes to the ER for peroxisome maintenance and lipid homeostasis. *J. Cell Biol.* **216**, 367–377 (2017)
FURTHER READING Phillips, M. J. & Voeltz, G. K. Structure and function of ER membrane contact sites with other organelles. *Nat. Rev. Mol. Cell Biol.* **17**, 69–82 (2016)

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