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ER-mitochondria signaling regulates autophagy

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ABSTRACT

The endoplasmic reticulum (ER) and mitochondria form tight functional contacts that regulate several key cellular processes. The formation of these contacts involves "tethering proteins" that function to recruit regions of ER to mitochondria. The integral ER protein VAPB (VAMP associated protein B and C) binds to the outer mitochondrial membrane protein, RMDN3/PTPIP51 (regulator of microtubule dynamics 3) to form one such set of tethers. Recently, we showed that the VAPB-RMDN3 tethers regulate macroautophagy/autophagy. Small interfering RNA (siRNA) knockdown of VAPB or RMDN3 to loosen ER-mitochondria contacts stimulates autophagosome formation, whereas overexpression of VAPB or RMDN3 to tighten contacts inhibit their formation. Artificial tethering of ER and mitochondria via expression of a synthetic linker protein also reduces autophagy and this artificial tether rescues the effects of *VAPB*- or *RMDN3*-targeted siRNA loss on autophagosome formation. Finally, our studies revealed that the modulatory effects of ER-mitochondria contacts on autophagy involve their role in mediating ITPR (inositol 1,4,5-trisphosphate receptor) delivery of Ca^{2+} from ER stores to mitochondria.

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Signaling between ER and mitochondria is now known to regulate several fundamental physiological functions. This signaling involves close physical contacts between the 2 organelles such that up to approximately 20% of the mitochondrial surface is closely apposed to ER membranes. The regions of ER in contact with mitochondria are termed mitochondria-associated membranes (MAMs). The mechanisms by which ER membranes are recruited to mitochondria are not properly known but one route involves binding of the integral ER protein VAPB to the outer mitochondrial membrane protein RMDN3. VAPB and RMDN3 thus act as molecular scaffolds to tether the 2 organelles.

Our recent studies showed that experimental manipulation of VAPB and RMDN3 expression to increase and decrease ER-mitochondria contacts markedly affects autophagy. Overexpression of VAPB or RMDN3 to tighten ER-mitochondria contacts, impairs basal and chemical (rapamycin and Torin1)-induced autophagy by decreasing autophagosome formation. In contrast, siRNA-mediated loss of VAPB or RMDN3 to loosen contacts causes an induction of autophagy flux with a concomitant increase in the number of autophagic structures. Importantly, this *VAPB* and *RMDN3* siRNA-mediated stimulation of autophagy is rescued by expression of a synthetic linker protein that artificially tethers ER and mitochondria. Thus, these effects of VAPB and RMDN3 manipulation on autophagy are a consequence of their ER-mitochondria tethering function and not some as yet unknown alternative function of VAPB and RMDN3.

Interestingly, we discovered that while tightening ER-mitochondria contacts by overexpression of VAPB or RMDN3 impairs rapamycin- and Torin1-induced autophagy, it does not affect autophagy induced by starvation. This suggests that the regulation of autophagy by ER-mitochondria signaling is at least partly dependent upon the nature of the autophagic stimulus. Rapamycin and Torin1 induce autophagy by selective inhibition of MTOR, whereas starvation-induced autophagy is a more complex mechanism involving a variety of other nutrient-sensing molecules. Thus, the different effects may be due to differences in the signaling mechanism by which these stimuli induce autophagy.

So how do the VAPB-RMDN3 tethers and ER-mitochondria signaling generate this effect on autophagy? A primary function of ER-mitochondria contacts is to facilitate ITPR-medited delivery of Ca^{2+} from ER stores to mitochondria via VDAC (voltage dependent anion channel) and MCU (mitochondrial calcium uniporter). This Ca^{2+} is required by mitochondria for efficient ATP production because several dehydrogenases in the TCA cycle are Ca^{2+}-dependent. Thus, overexpression of VAPB or RMDN3 to tighten ER-mitochondria contacts enhances, whereas siRNA loss of VAPB or RMDN3 to loosen contacts inhibits Ca^{2+} exchange. A number of previous studies have shown that disruption of ITPR-mediated Ca^{2+} delivery stimulates autophagy. Consistent with these findings, we found that blocking ER-mitochondria Ca^{2+} exchange via ITPR antagonists or *MCU*-targeted siRNAs abrogate the effects of VAPB

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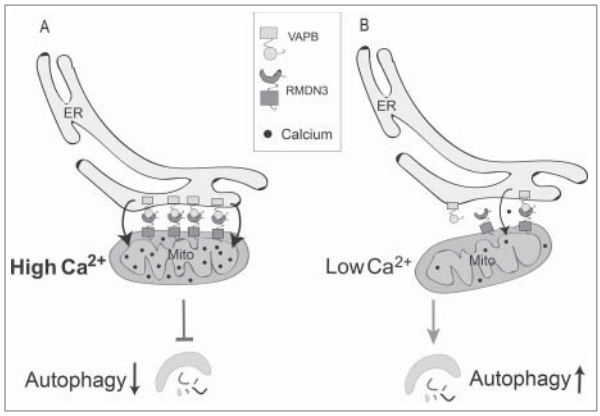

Figure 1. Diagram illustrating the proposed mechanism by which the VAPB-RMDN3 ER-mitochondria tethering complex regulates autophagy. (A) VAPB or RMDN3 overexpression tightens ER-mitochondria contacts to enhance ITPR-mediated Ca^{2+} delivery to mitochondria, which in turn inhibits autophagosome formation. (B) siRNA-dependent loss of VAPB or RMDN3 loosens ER-mitochondria contacts to inhibit Ca^{2+} delivery and stimulate autophagosome formation.

and RMDN3 overexpression on autophagy. Thus the mechanism by which the VAPB-RMDN3 tethers regulates autophagy involves their role in facilitating ER-mitochondria Ca^{2+} exchange.

A number of recent studies have demonstrated that damage to ER-mitochondria signaling occurs in neurodegenerative diseases such as Alzheimer and Parkinson diseases, and frontotemporal dementia with related amyotrophic lateral sclerosis. Dysregulation of autophagy has also been linked to these disorders. Our findings will therefore facilitate future investigations on the role of autophagy in neurodegenerative diseases.

Disclosure of potential conflicts of interest

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