

c-FLIP_L regulates endoplasmic reticulum morphology and mitochondria-associated membranes functions

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Physical and functional interactions between endoplasmic reticulum (ER) and mitochondria take place at the mitochondria-associated membranes (MAMs), ER sub-domains at the interface between the two organelles. Protein complexes at MAMs regulate lipid synthesis, Ca²⁺ signaling and apoptosis¹. Furthermore, they influence both ER and mitochondrial morphology, as their ablation is frequently associated to the dramatic remodeling of these organelles. Here we show that c-FLIP_L (cellular FLICE-inhibitory protein, long isoform), mainly known as inhibitor of caspase-8, can be retrieved at the ER and MAMs. c-FLIP ablation in mouse embryonic fibroblasts (MEFs) impairs ER morphology and luminal contiguity, by inducing the proliferation of ER cisternae to the detriment of tubular ER. Furthermore, c-FLIP_L controls the ER-mitochondria apposition, as the depletion of this protein physically uncouples the two organelles. Moreover, functionally, c-FLIP ablation lowers the cytosolic Ca²⁺-increase evoked either by agonists stimulation or by passive ER discharge and increases the resistance of c-FLIP^{-/-} cells to ER stress-induced apoptosis. We also report that c-FLIP^{-/-} cells show an increased caspase-mediated cleavage of the ER-shaping protein Reticulon-4 (which is a well-known regulator of ER biogenesis and morphology), at both basal level and upon TNF α -dependent apoptosis. In agreement with these findings, we finally show that c-FLIP absence enhances basal caspase-8 activation in c-FLIP^{-/-} MEFs and that caspase-8 inhibition reverts morphological alterations in ER shape observed in c-FLIP^{-/-} cells, suggesting a novel role for caspase-8 and c-FLIP_L as regulators of ER functions and ER-mitochondria crosstalk.

References

- [1] de Brito, O. M. and L. Scorrano (2010) An intimate liaison: spatial organization of the endoplasmic reticulum-mitochondria relationship. *EMBO J* 29(16): 2715-2723.

Keywords

Endoplasmic reticulum; mitochondria-associated membranes; caspase-8; c-FLIP; Reticulon-4.