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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 subdomains at the interface between the two organelles. Protein complexes at MAMs regulate lipid synthesis, Ca^{2+} signaling and apoptosis [1]. 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 Ca^{2+}-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 TNFα-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

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