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A novel role of c-FLIP protein in regulation of ER stress response

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Cellular-Flice-like Inhibitory Protein (c-FLIP) is an apoptosis modulator known to inhibit the extrinsic apoptotic pathway thus blocking Caspase-8 processing in the Death Inducing Signalling Complex (DISC). We previously demonstrated that c-FLIP localizes at the Endoplasmic Reticulum (ER) and that c-FLIP-deficient Mouse Embryonic Fibroblasts (MEFs) display an enlarged ER morphology. In the present study, we have addressed the consequences of c-FLIP ablation in the ER stress response by investigating the effects of pharmacologically-induced ER stress in Wild Type (WT) and c-FLIP-/- MEFs. Surprisingly, c-FLIP-/- MEFs were found to be strikingly more resistant than WT MEFs to ER stress-mediated apoptosis. Analysis of Unfolded Protein Response (UPR) pathways revealed that Pancreatic ER Kinase (PERK) and Inositol-Requiring Enzyme 1 (IRE1) branch signalling is compromised in c-FLIP-/- cells when compared with WT cells. We found that c-FLIP modulates the PERK pathway by interfering with the activity of the serine threonine kinase AKT. Indeed, c-FLIP-/- MEFs display higher levels of active AKT than WT MEFs upon ER stress, while treatment with a specific AKT inhibitor of c-FLIP-/- MEFs subjected to ER stress restores the PERK but not the IRE1 pathway. Importantly, the AKT inhibitor or dominant negative AKT transfection sensitizes c-FLIP-/- cells to ER stress-induced cell death while the expression of a constitutively active AKT reduces WT cells sensitivity to ER stress-induced death. Thus, our results demonstrate that c-FLIP modulation of AKT activity is crucial in controlling PERK signalling and sensitivity to ER stress, and highlight c-FLIP as a novel molecular player in PERK and IRE1-mediated ER stress response.