ER stress signaling and the BCL-2 family of proteins: From adaptation to irreversible cellular damage

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Programmed cell death is essential for the development and maintenance of cellular homeostasis, and its deregulation results in a variety of pathologic conditions. The BCL-2 family of proteins is a group of evolutionarily conserved regulators of cell death that operate at the mitochondrial membrane to control caspase activation. This family is comprised both of antiapoptotic and proapoptotic members, in which a subset of proapoptotic members, called BH3-only proteins, acts as upstream activators of the core proapoptotic pathway. In addition to their known role at the mitochondria, different BCL-2-related proteins are located to the endoplasmic reticulum (ER) membrane, where new functions have been recently proposed. In this review, evidence is presented indicating that members of the BCL-2 protein family are contained in multiprotein complexes at the ER, regulating diverse cellular processes including autophagy, calcium homeostasis, the unfolded-protein response, ER membrane remodeling