

A BAX/BAK and cyclophilin D-independent intrinsic apoptosis pathway

Zamorano, Sebastián

Rojas-Rivera, Diego

Lisbona, Fernanda

Parra, Valentina

Court, Felipe A.

Villegas, Rosario

Cheng, Emily H.

Korsmeyer, Stanley J.

Lavandero, Sergio

Hetz, Claudio

Most intrinsic death signals converge into the activation of pro-apoptotic BCL-2 family members BAX and BAK at the mitochondria, resulting in the release of cytochrome c and apoptosome activation. Chronic endoplasmic reticulum (ER) stress leads to apoptosis through the upregulation of a subset of pro-apoptotic BH3-only proteins, activating BAX and BAK at the mitochondria. Here we provide evidence indicating that the full resistance of BAX and BAK double deficient (DKO) cells to ER stress is reverted by stimulation in combination with mild serum withdrawal. Cell death under these conditions was characterized by the appearance of classical apoptosis markers, caspase-9 activation, release of cytochrome c, and was inhibited by knocking down caspase-9, but insensitive to BCL-XL overexpression. Similarly, the resistance of BIM and PUMA double deficient cells to ER stress was reverted by mild serum withdrawal. Surprisingly, BAX/BAK-independent cell death did not require Cyclophilin D (CypD) e