Apoptosis induced by direct triggering of mitochondrial apoptosis proceeds in the near-absence of some apoptotic markers.

Abstract:

Apoptotic cell death is characterized by the activation of the apoptotic signal transduction pathway on one hand and a number of regularly found morphological and biochemical features, such as nuclear condensation and mitochondrial depolarisation. Although much of our knowledge of apoptosis was obtained using noxious stimuli in cell culture, these apoptotic stimuli are likely to have numerous off-target effects that may contribute to or obscure the immediate effects of the apoptotic pathway. We have developed a cellular model where mitochondrial apoptosis is directly triggered by the tetracycline-regulated expression of the pro-apoptotic BH3-only protein Bim(S). We report the comparison of Bim(S)-induced apoptosis with the commonly used apoptotic stimuli staurosporine and UV-light. While the release of mitochondrial cytochrome c and Smac/DIABLO, activation of caspases and nuclear morphological changes occurred with very similar kinetics, striking differences were found in other apoptotic assays. In particular, drop in mitochondrial membrane potential, loss of plasma membrane integrity and the appearance of sub-G1 nuclei were strongly reduced in cells dying upon Bim(S)-induction, compared to staurosporine- or UV-induced apoptosis. The results thus indicate that the link between the apoptotic pathway and commonly used indicators of apoptosis is less tight than it appears from experiments with
cytotoxic stimuli.

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