Are tilted peptides in Bax and Bak responsible for mitochondrial permeability during apoptosis ?

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Apoptotic cell death is regulated by three subfamilies of Bcl-2 proteins. Bax and Bak are members of a pro-apoptotic subfamily that lies at the center of apoptosis regulation, as cells lacking both Bax and Bak are highly resistant to most apoptotic stimuli, including expression of other pro-apoptotic Bcl-2 proteins. Bax and Bak mediate apoptosis by permeabilizing the mitochondrial outer membrane following which intermembrane space proteins such as cytochrome c move to the cytosol and activate caspases, leading to the cleavage of multiple cellular proteins and organized demise of the cell.

The mechanism by which Bax and Bak mediate mitochondrial permeability remains unclear, but is often associated with Bax and Bak conformational changes, insertion into the membrane, oligomerization, and binding to other proteins. Various membrane changes associated with Bax and Bak activation include changes in membrane curvature and the formation of lipid pores.

The structure of Bax is similar to that of the anti-apoptotic proteins Bcl-2 and Bcl-x_L, affording no explanation for their opposite functions. We thus considered whether the membrane permeabilizing effects of Bax and Bak might be due to the presence of tilted peptides, i.e. alpha helices that orientate in an oblique fashion in lipid bilayers. Based on the structures of Bax, Bcl-2 and Bcl-x_L, each of these proteins together with Bak (3D structure predicted by homology to Bax) was analyzed by computational analysis (IMPALA) for the presence of potential tilted peptides. Interestingly, this analysis predicted the presence of a tilted helix in both Bax and Bak that was not present in either Bcl-2 or Bcl-x_L. We are currently testing this functionally by reconstituting Bax/Bak double knockout cells with Bax and Bak mutants containing an equivalent non-tilted helix, and testing for re-sensitization to apoptosis.