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Crystal structures of Bax and Bak Reveal Molecular Events Initiating Apoptosis

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A key event in apoptosis is the conversion of Bax or Bak from inert monomers into cytotoxic mitochondrial membrane perforating oligomers. Certain BH3-only relatives can initiate this step through direct interactions, yet the means by which conformational changes are invoked, the nature of the conformational changes themselves, the mechanism by which they insert into membranes and the process by which they perforate these barriers has largely remained a mystery. Our recent structural studies provided the first insights into this process for Bax [1]. We found that BH3 domains activate Bax by binding to a hydrophobic groove on its surface. Crystal structures of these complexes revealed an unexpected conformational change involving dissociation of a previously unrecognized “core” domain from a “latch’ domain. A further structure of the freed Bax “core” domains revealed that these form dimers that possess a surface of aromatic residues which we hypothesis engage the outer leaflet of the mitochondrial membrane and induce curvature. We have now extended our studies to include structures of Bax bound to alternative BH3-only proteins providing new insights into key interactions occurring at this interface. Additionally, we have solved structures of activated Bak and of the freed Bak “core” domain dimers. These results further our understanding of the molecular mechanisms by which these highly dynamic proteins engage the mitochondrial membrane and thus control the life/death switch in cells.

[1] *P. Czabotar, D. Westphal, G. Dewson et al., Cell, 2013, 152, 519-531*

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