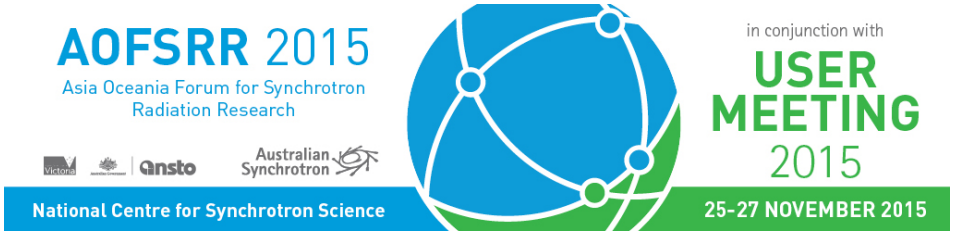

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Structural Investigation of Bax Oligomerisation

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The Bcl-2 protein family regulates the intrinsic apoptotic pathway and the critical step of mitochondrial outer membrane permeabilisation (MOMP). MOMP results in the release of Cytochrome *c* and other molecules from the intermembrane space, leading to the formation of the apoptosome and caspase activation. Bax and Bak are structurally and functionally homologous pro-apoptotic Bcl-2 proteins that facilitate MOMP. BH3-only proteins such as Bim transiently bind to and activate Bax and/or Bak resulting in their homodimerisation and oligomerisation. The large Bax/Bak oligomers disrupt the mitochondrial outer membrane causing MOMP. BH3-only protein binding causes the dissociation of Bax/Bak into two distinct domains known as the "core" and "latch" domains. The structures of both homodimerised Bax and homodimerised Bak core domains, with a GFP fusion tag to aid crystallisation, have been solved. The core domains dimerise through a symmetrical interface involving the reciprocal insertion of the BH3 domain alpha helix of one Bax/Bak molecule into the hydrophobic groove of the partner Bax/Bak molecule. To further investigate the Bax core domain, we have expressed it as a GST fusion protein and removed the GST tag. The cleaved core domain remains soluble and runs as a multimer (likely a hexamer or an octamer) on a size exclusion column. The structure of this multimer could provide insight into the nature of the large Bax oligomers that have remained structurally enigmatic despite decades of investigation.

Keywords

Apoptosis Bcl-2 Bax Bak

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