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Structural Insights into Bak Activation and Oligomerisation

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Apoptotic stimuli activate and oligomerise the pro-apoptotic proteins Bak and Bax resulting in mitochondrial outer membrane permeabilisation and subsequent cell death. Crystal structures by Czabotar et al. (2013) provided novel insights into BH3-only induced Bax activation and oligomerisation, namely the separation of the core and latch domains, followed by core domain dimerisation. Here we provide complementary studies on the related protein Bak. We present the crystal structures of Bak core-latch domain swapped dimers and demonstrate their dissociation upon Bak activation. A second crystal structure of the Bak core domain provides the first high-resolution details for this key dimerisation unit upon which the larger Bak oligomer builds. Cellular assays, guided by the presented crystal structures, confirm the physiological relevance of these key events in the intrinsic apoptotic pathway (Brouwer et al. 2014). These studies confirmed an analogous mechanism for activation and dimerization of Bak and Bax in response to BH3-only peptides. More recently we have performed structural studies on the direct interaction of BH3-only peptides with Bak. We have gained insight into the differences between interactions of BH3 only proteins with Bak compared to the pro-survival proteins; this may inform the design of novel therapeutics to manipulate cell death.

References

Brouwer et al. (2014), Mol Cell, published online 28th August, <http://dx.doi.org/10.1016/j.molcel.2014.07.016>

Czabotar et al. (2013), Cell 152(3): 519-531.

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