MS12 Biophysical characterization and crystallization

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MS12-P1 Structural and Functional Characterisation of Bok, a Pro-apoptotic Bcl-2 Effector Protein

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The Bcl-2 protein family regulates the essential cell death program known as intrinsic or mitochondrial apoptosis. A delicate balance of pro-survival and pro-apoptotic Bcl-2 proteins controls the critical process of mitochondrial outer membrane permeabilisation (MOMP) that results in the release of Cytochrome *c* from the intermembrane space and the subsequent death of the cell.

The pro-apoptotic effector proteins Bax and Bak facilitate MOMP and are kept in check by pro-survival proteins such as Mcl-1, Bcl-X_L and the founding member and namesake of the family, Bcl-2. Pro-apoptotic BH3-only proteins such as Bim and Bid can both directly activate Bax and Bak and inhibit the function of pro-survival proteins. When pro-surivival proteins are overwhelmed due to upregulation of BH3-only proteins in response to stress signals, activated Bax and Bak oligomerise on the mitochondrial outer membrane leading to MOMP.

Until recently, Bax and Bak were thought to be absolutely required for MOMP. However, recent work from the lab of Douglas Green has identified the previously enigmatic Bcl-2 protein Bok as a bone fide pro-apoptotic effector protein with the ability to permeabilise the mitochondria as well as membrane-mimicking liposomes. Interestingly, in contrast to Bax and Bak, Bok appears to be constitutively active and regulated by ER-associated degradation rather than by other Bcl-2 proteins.

We have solved the X-ray crystal structure of a homolog of human Bok that may provide clues in regards to its atypical property of constitutive activation. Additionally, we have performed our own biophysical characterization of Bok using a liposomal system and surface plasmon resonance. We find that, in agreement with recently published work, Bok is constitutively active and interacts only weakly with other Bcl-2 proteins.

Keywords: Bcl-2, apoptosis, Bok