

Structures of Mcl-1 in complex with the Bim and Noxa BH3 domains

P. E. Czabotar¹, E. F. Lee^{1,2}, M. F. Van Delft^{1,2}, C. L. Day³, B. J. Smith¹, D. C.S. Huang⁴, W. D. Fairlie¹, M. G. Hinds¹, P. M. Colman¹

¹*Structural Biology, Walter & Eliza Hall Institute for Medical Research, Parkville, VIC, Australia*

²*Department of Medical Biology, University of Melbourne, Parkville, VIC, Australia*

³*Department of Biochemistry, University of Otago, Dunedin, New Zealand*

⁴*Molecular Genetics of Cancer, Walter & Eliza Hall Institute for Medical Research, Parkville, VIC, Australia*

The Bcl-2 family of proteins are important in the regulation of apoptosis. The family consists of two main groups: the pro-survival group, of which Mcl-1 is a member, inhibit apoptosis; the pro-apoptotic group, of which Noxa and Bim are members, initiate apoptosis. Interactions between members of these groups are important for determining whether a cell lives or dies. All members of the Bcl-2 family contain a number of Bcl-2 homology (BH) domains. These domains are involved in interactions between family members. In particular, the BH3 domain of pro-apoptotic proteins interacts with a groove composed of the BH1, BH2 and BH3 domains of pro-survival proteins. It has recently been demonstrated that Noxa and Bim are important binding partners for Mcl-1. Mcl-1 function is also regulated by proteasomal degradation. Binding of Noxa to Mcl-1 targets it for degradation. In contrast binding to either Bim stabilises Mcl-1 levels. Here we describe the crystal structures of the hMcl-1:hBim BH3 complex and the hMcl-1:mNoxaB BH3 complex. These provide important insights into the structural signal for Noxa-induced degradation of Mcl-1.