SEMINAR

Department of Biological Sciences

NUS National University of Singapore

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Hosted by A/P Henry Mok

DEATH is not an option – structural insight into virus mediated inhibition of apoptosis

Viruses must evade host apoptotic defences to ensure their own survival. Despite the complexity of mammalian cell death processes, viruses have evolved successful mechanisms for subverting the apoptotic machinery, including homologs of the mammalian pro-survival protein Bcl-2. We have studied the potent anti-apoptotic virulence factor F1L, which has previously been shown to be a critical factor for subversion of initial host cell apoptosis during vaccinia virus infection. We show that F1L adopts a Bcl-2 like fold despite sharing no discernible sequence identity with cellular Bcl-2 proteins, and unexpectedly forms a dimer in solution. We have also determined crystal structures of F1L in complex with BH3 domain peptides from its main biologically relevant ligands, Bim and Bak. Using our structures as a guide we employed site-directed mutagenesis to generate a panel of F1L binding grove mutants to investigate the relative contributions of each of the main F1L pro-death ligands.

A second anti-apoptotic factor of interest is BHRF1 from the ubiquitous Epstein-Barr virus (EBV), a member of the gamma-herpesviruses, that has been implicated in the development of certain malignancies including Burkitt lymphoma and nasopharyngeal carcinoma. We show that BHRF1 is a potent inhibitor of apoptosis, and confers chemoresistance in mouse lymphoma models similar to mammalian Bcl-2. Next, we determined the crystal structures of BHRF1 in complex with Bim and Bak BH3 peptides and show that in contrast to previous predictions, BHRF1 interactswith these proteins in a manner similar to its mammalian counterparts. Structure-based mutagenesis enabled us to address the molecular mechanisms underlying BHRF1 activity. Our studies indicate that BHRF1 might be targeted by small molecule mimetics of BH3-only proteins.

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His brief biosketch:
Marc obtained a PhD in Crystallography at the end of 2003 from Imperial College London, UK, studying protein-protein interactions in the extracellular matrix with Prof. Erhard Hohenester. In 2004 he joined Prof. Peter Colman's laboratory at the Walter & Eliza Hall Institute (WEHI) in Melbourne as a Leukemia & Lymphoma Society of America Fellow. He spent 5 years at WEHI studying the interactions of viral proteins with the mammalian cell death machinery. In 2010 Marc took up a position asLaboratory Head and NHMRC CDA Fellow at the Department of Biochemistry, School of Molecular Sciences, La Trobe University, where he has now established a structural biology community as part of the soon to be opened La Trobe Institute of Molecular Science (LIMS). His laboratory is chiefly interested in protein:protein interactions at the host:pathogen interface, as well as in the development of therapeutics to modulate the activity of pathogen derived factors.

Artwork by Ann Nee, DBS, NUS