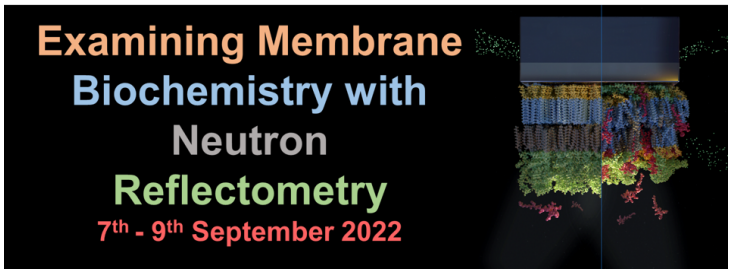

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Unravelling Bcl-2 proteins´ functioning at mitochondrial membrane level

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Programmed cell death (apoptosis) is essential for human life. In its intrinsic apoptotic pathway opposing members of the B-cell lymphoma 2 (Bcl-2) protein family control the permeability of the mitochondrial outer membrane (MOM) and any release of apoptotic factors. Any imbalance can cause disorders including cancer, where often upregulation of cell protecting (anti-apoptotic) Bcl-2 members such as the Bcl-2 membrane protein itself plays a notorious role by blocking membrane perforating apoptotic proteins such as Bax which normally will cause cell death. Here, we apply neutron reflectometry (NR) on supported lipid bilayers which mimic MOM environment and solid state/liquid state NMR spectroscopy to unravel the molecular basis driving opposing proteins to interact with each other at the MOM; a mechanism which is not really understood yet due to lack of high-resolution structural insight. Based on our central hypothesis that Bcl-2 drives its cell-protecting function at a membrane-embedded location as revealed by NR (1), we focus i) to determine the structure of human Bcl-2 protein in its membrane setting by combining solution and solid-state NMR; ii) use NR to study the kinetics and lipid/protein pore assemblied upon binding of Bax to mitochondrial membranes and its membrane destroying activities there; and iii) unravel the nature of direct interaction between Bcl-2 and Bax to neutralize each other. Knowledge generated here, will be indispensable in understanding the regulative function of the Bcl-2 family at mitochondrial membranes.

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