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Interaction of Prohibitin with the inner of mitochondrial membrane

Prohibitins (PHB) are highly conserved heterodimeric proteins composed of two subunits PHB1 and PHB2 arranged to make a multimeric ring at the inner mitochondrial membrane [1]. They play a crucial role in premature cellular ageing, tumour suppression, cell cycle regulation, apoptosis, and mitochondrial homeostasis via their function in the intermembrane space (IMS) of mitochondria (between the inner and outer membranes).
Despite the essential role of this complex, little is known regarding its molecular structure and arrangement within the membrane. Initial reports suggest that the formation of the prohibitin complex is influenced by the action of cardiolipin (CL), which is involved in maintaining a particular shape and curvature of the inner mitochondrial membrane [2].
The two main aims of this project are to (i) characterize the interaction between the N-terminal helices of PHB (NT-PHBx) with the membrane and establish a possible synergy of the two PHB homologues, and (ii) understand the role of cardiolipin in this interaction.
To answer these questions, we employ both interface and bulk techniques on simplified model systems, using synthetic peptides corresponding to the transmembrane domains of PHB (NT-PHB, 20-24 residues long), and synthetic or natural mixtures of lipids. As interfacial techniques exploring the solid/liquid interface, we apply Neutron Reflectometry (NR) and Quartz-crystal microbalance with dissipation monitoring (QCM-D). As bulk techniques are used to extruded liposomes we employ Small-Angle Scattering by X-rays and Neutrons (SAXS, SANS).
NR and QCM-D preliminary results suggested a higher tendency of NT-PHB1 of insertion into the membrane in the presence of CL, while NT-PHB2 can remove lipid from the bilayer in absence of CL. Due to the amphipathic character, NT-PHB2 seems to puncture the membrane.
SANS is employed to evaluate the in-solution structure, studying the effect of the peptides on the vesicles, and focusing on the liposomes. Preliminary SANS results show that the peptide induces fusion of the vesicles, from multilamellar to unilamellar vesicles, indicating a tendency of the peptides to disrupt the membrane.

[1] S. Mishra, L. C. Murphy, B. L. G. Nyomba, and L. J. Murphy, “Prohibitin: A potential target for new therapeutics,” Trends Mol. Med., vol. 11, no. 4, pp. 192–197, 2005.
[2] E. Beltrán-Heredia, F.-C. Tsai, S. Salinas-Almaguer, F. J. Cao, P. Bassereau, and F. Monroy, “Membrane curvature induces cardiolipin sorting,” 2019.

Primary author: PICCININI, Alice (Institut Laue-Langevin)

Co-authors: PREVOST, Sylvain (Institut Laue-Langevin); WINTER, Anja (Keele University)

Presenter: PICCININI, Alice (Institut Laue-Langevin)