Interaction of Prohibitin with m-AAA proteases at the inner of mitochondrial membrane

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Prohibitin (PhB) are highly conserved heterodimer proteins [1] [2] that play a role in premature cellular ageing and apoptosis via their function in the intermembrane space (IMS) of mitochondria (between the inner and outer membranes). They help maintaining a healthy mitochondrial morphology and cellular metabolic capacity by interacting with m-AAA proteases contained within the inner mitochondria space. The deregulation of this protein complex is involved in viral infections, neurological diseases and cancer. Despite the essential role of this complex, little is known regarding its structure. The formation of the Prohibitin complex is influenced by the action of cardiolipin (CL) mostly present in the inner mitochondrial membrane, participating to the particular shape and curvature of this membrane.[3]

Two of the aims of this thesis project are (i) to characterize the interaction of the N-terminal helices with the mitochondrial membrane and detect a possible synergy of the simultaneous presence of both N-terminal groups (PhB1 and 2) and (ii) understand the role of cardiolipin. These goals are currently undertaken with simplified models, using short (20-24 amino acids) peptides and membranes with various but simple lipidic composition.

The analysis of the insertion of peptides in the membrane is carried out with surface techniques on flat bilayers: namely neutron reflectometry (NR) and Quartz-Crystal-Microbalance with dissipation monitoring (QCM-D), and complemented with a bulk technique on liposomes (closed curved bilayer): small angle neutron scattering (SANS).

Preliminary results show a higher tendency of the PhB1 peptide for insertion, whatever the membrane composition, i.e. CL is not essential for this interaction although it may influence it. We are currently testing various structural models to understand in detail the peptide incorporation into the bilayer as a function of the membrane properties, and we plan to study next membranes with full lipid composition extracted from natural source.

References:

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