Investigating the VDAC:Bcl2 complexes implicated in apoptosis using Double Electron-Electron Resonance

Keywords
Apoptosis ; VDAC ; Bcl2-family ; pulse-EPR (DEER) ; Gadolinium

Summary
Apoptosis is a highly regulated process playing a role in numerous biological events, including development, aging and many disorders (cancer, Alzheimer). Mitochondria-mediated apoptosis involves release of cytochrome c (cyt c) across the Mitochondrial Outer Membrane (MOM), triggering the caspase cascade and leading to cell death. This release is tightly regulated by the Bcl2-family pro-apoptotic proteins Bax, Bak and tBid, that need to be activated and integrated to the MOM to induce MOM permeation. Despite decades of research, the molecular mechanism behind this crucial step remains elusive, but a precise comprehension is essential to the development of new drug classes of apoptosis modulators, as well as more efficient and potent cancer therapies (Bcl2 mimetics were approved by the US FDA for the treatment of lymphocytic leukaemia[1]). The Voltage-Dependent Anion Channel (VDAC) is the most abundant protein in the MOM, governing the flux of ions and metabolites between the mitochondria and the cytosol. Several in vivo studies have shown that interactions between VDAC2 and the pro-apoptotic proteins Bax, Bak, or tBid are necessary to trigger MOM permeation[2–4]. Nevertheless, the precise role of VDAC in this process remains to be understood. Is VDAC needed for insertion of Bcl2 proteins in the membrane, for their activation, or for both? Biochemical and structural characterizations of VDAC:Bcl2 interactions are missing, but essential to answer these questions. This project aims to study complexes between VDAC2 and the pro-apoptotic proteins Bax and tBid, and characterize them both biochemically and structurally using Double Electron-Electron Resonance (DEER). Very limited data is available on the role of VDAC2 in cyt c permeation. The characterization of the interaction between VDAC and Bax/tBid, and the possible activation of Bcl2 proteins by VDAC2 are critical to understand this key event of apoptosis.

References:
1. Roberts A. et *al. Clin. Pharmacol. Ther.* (2017). 2. Naghdi, S. et *al. PNAS.* (2015). 3. Chin, H. *et al. Nat. Commun.* (2018). 4. Lauterwasser, J. *et al. Sci. Rep.* (2016)

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Location
LISM and BIP, 31 chemin Joseph Aiguier Marseille, France

Doctoral school
Life and Health Sciences (ED 62), Aix-Marseille université (https://ecole-doctorale-62.univ-amu.fr/)

Expected profile of the candidate
The candidate should be rigorous, motivated and have a master's or engineering degree. The student must be familiar with protein biochemistry and biophysics, experience with EPR or NMR will be a plus.