STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF THE DISEASE-LINKED INNER MITOCHONDRIAL MEMBRANE PROTEIN MPV17

The membrane protein MPV17 localized in the inner mitochondrial membrane is one of the causes of the so-called "mitochondrial DNA depletion" syndrome (MDDS), i.e. the reduction of the amount of DNA in the mitochondrial matrix. Since the essential components of the respiratory chain are encoded on mitochondrial DNA, mutations in the MPV17 gene lead to severe liver damage and hepatocerebral dysfunction, and thus usually to death in early infancy. The function and mechanistic details of MPV17 are relatively poorly understood, limiting therapies to the treatment of symptoms. In this project, we aim to better understand the molecular causes of MPV17-related diseases. We will first elucidate whether MPV17 is a transporter of metabolites, e.g. precursors of nucleic acids. For this purpose, the direct binding of metabolites to MPV17, but also the effect of deletion of MPV17 on the mitochondrial metabolome will be investigated. A potential role of MPV17 as a voltage-gated proton channel will also be investigated, which would lead to a reduction of the membrane potential when the respiratory chain is overloaded, thus reducing the formation of reactive oxygen species (ROS) and damage to the cell, including the mitochondrial DNA. MPV17 has been also associated with the stabilization of mitochondrial cristae, which is directly linked to respiratory chain efficiency. To investigate this potential function, we will perform cryo-electron tomography studies using MPV17-knockout cells. With the high spatial resolution this provides an accurate picture of the location of MPV17 and its potential involvement in the cristae. MPV17 appears to be activated by oxidative conditions. Therefore, we will perform our functional studies under high ROS stress conditions, which may lead to oxidation of the cysteine residues in MPV17, inducing structural changes. In the second part of the study, the three-dimensional structure of MPV17 will be obtained by NMR spectroscopy and cryo-electron microscopy. The monomer at reducing conditions will be studied by NMR spectroscopy, and the oligomer populated at oxidative conditions will be studied by cryo-electron microscopy to better understand the mechanism of MPV17 activation. With the obtained structural information, the influence of mutations on MPV17 function can be better understood, which is the basis for a specific therapy of MPV17-induced MDDS.

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Proposed collaboration within ArchiFun network (not mandatory at this stage): -

Proposed list of secondments (not mandatory, but recommended if known already):
European Synchrotron Radiation Facility, Grenoble, France
Nanotemper Technologies GmbH, Germany
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Main ArchiFun theme involved:

Mechanisms of bacterial resistance and cancer onsets;

Neurodegenerative and autoimmune diseases;