1. Supervision

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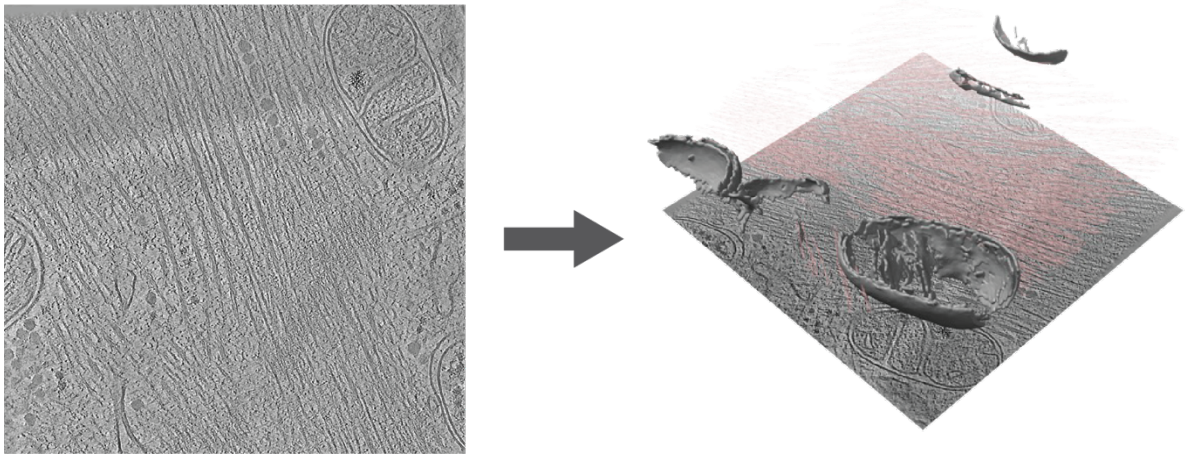
2. Title of Master Thesis's Project

Visualizing the effect of MPV17 deletion on mitochondrial structure by *in situ* cryo-electron tomography



3. Project Description

MPV17 is an inner mitochondrial membrane protein whose dysfunction has been linked to mitochondrial DNA depletion syndrome, a disease connected to human mitochondrial DNA maintenance defects (MDMD)[1,2]. Around 50 different gene mutations were reported in MPV17 in about 100 patients, leading to hepatocerebral malfunction, such as liver failure, in early infants[3-5]. In a few cases, mutation in MPV17 resulted in a later-onset neuromyopathic disease with a better prognosis[6-8], suggesting that the clinical outcome correlates with the location of mutations in the MPV17 gene. However, for MPV17 the exact function and underlying pathomechanism is unresolved and the therapy remains merely symptomatic. The protein is known to be crucial for mtDNA maintenance by conserving a balanced mitochondrial nucleotide pool, and therefore has been suggested to act as a transporter for dNTP precursors[3,9]. More

recently, a role of MPV17 in the stabilization of mitochondrial cristae has been proposed in zebrafish[10], leading to markedly impaired mitochondrial functionality. MPV17 deficiency has been shown to result in a reduction of dNTPs and DNA in mitochondria[3,11,12], whereas its overexpression appears to have a protective role in preventing liver failure[13].

Building on our previous work[14], in parallel to structural investigations on purified MPV17 by NMR and cryo-EM, the cellular impact of MPV17 deletion in human knockout cell lines will be investigated by cryo-electron tomography (cryo-ET). Cryo-ET is a state-of-the-art imaging technique allowing to directly visualize macromolecules “in situ”, i.e., within the native cellular environment[15]. First, the cells are vitrified by rapid cooling, inducing a state of suspended animation. Next, a focused ion beam system is used to prepare thin sections free of artifacts, followed by cryo-ET imaging to obtain 3D volumes, called tomograms, of unperturbed cellular landscapes with molecular resolution[15].

This master thesis project will provide novel insights on the role of MPV17 in the formation and stabilization of mitochondrial cristae, which is essential for efficient ATP production in the respiratory chain in mitochondria. We are looking for a candidate with a solid background in biochemistry and biophysics, who can conduct cell culture experiments, sample preparation for cryo-ET, and the downstream data/image analysis.

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