Protein and lipid determinants of mitochondrial membrane fusion

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Mitochondria are double-membrane bound organelles that constantly move, fuse and divide within cells. The balance between fusion and fission events defines mitochondrial morphology and is crucial for normal mitochondrial and cellular function[1]. Outer mitochondrial membrane fusion is mediated by Mitofusin proteins whose molecular architecture consists of an N-terminal GTPase domain, a first heptad repeat domain (HR1), a transmembrane (TM) region, and a second heptad repeat domain (HR2). Mutations in any of these functional domains impair Mitofusin function, but their exact role in mitochondrial fusion remains elusive[2].

In vitro and *in situ* studies by us and others[3,4] suggest that the HR2 domain of Mitofusins mediates short distance (~10 nm) membrane docking by forming homotypic antiparallel dimers, while its HR1 domain – owing to its amphipathic nature – triggers fusion by perturbing the membrane structure (Fig. 1, left). It is now necessary to address how the GTPase domain collaborates with the heptad repeat domains during mitochondrial docking and fusion. Mitochondrial fusion is also regulated by specific lipids such as cardiolipin (CL), phosphatidylethanolamine (PE) and phosphatidic acid (PA)[5]. However, the exact mode of action of these regulatory lipids in Mitofusin-mediated fusion is not fully understood.

This PhD project aims at elucidating the molecular mechanisms by which Mitofusins mediate mitochondrial fusion and how this process is regulated by specific lipids. To this end, we will use a combination of approaches including cell-free *in vitro* membrane fusion assay, live cell imaging of mitochondrial fusion *in situ*, and morphological analysis of mitochondria by electron microscopy. The project will be done in close collaboration with Mickael Cohen, whose lab is at the forefront of research on cell biology and high resolution imaging of mitochondrial docking and fusion[6] (Fig. 1, right).

Applicants should hold a Master's degree in biochemistry, biophysics or molecular and cellular biology. To apply, please send a single PDF file that contains a CV, a short statement of research interests and experience, and three names of references with contact information to: david.tareste@inserm.fr (deadline: July 31st 2021).

References

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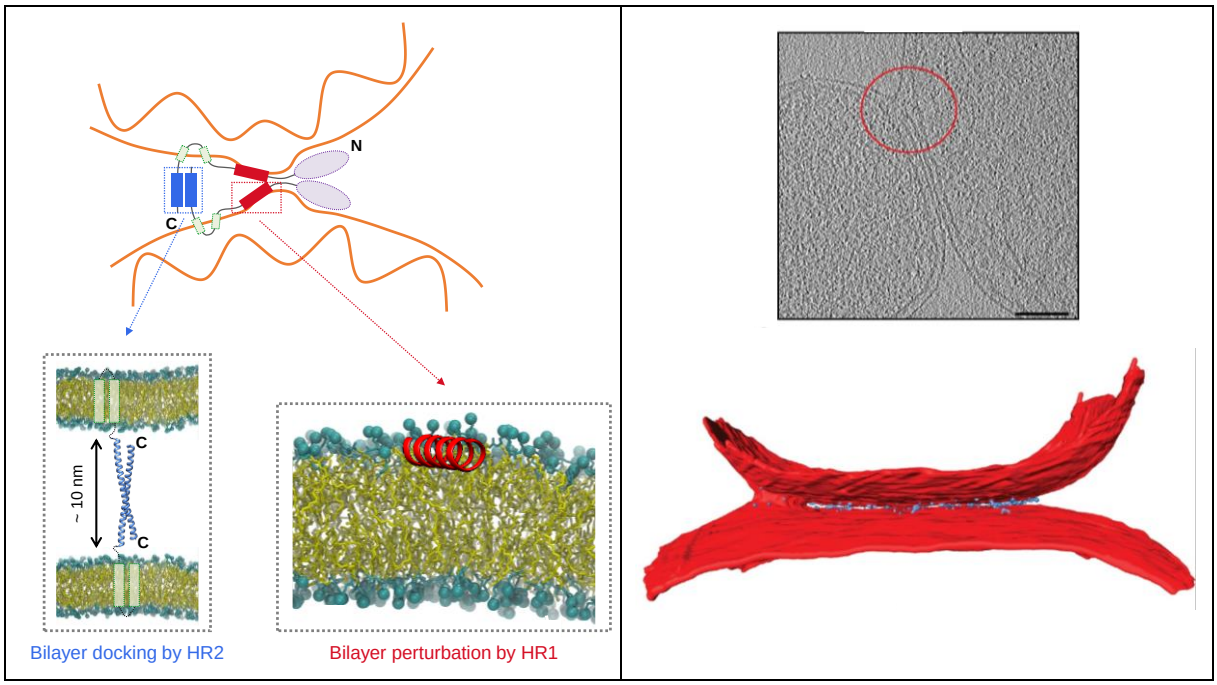

Figure 1. (Left) Working model for the role of the heptad repeat domains of Mitofusin in mitochondrial fusion[4]. (Right) Cryo-electron tomography picture of two docked mitochondria (the bar is 100 nm) showing that fusion is initiated at the edge of a Mitofusin docking ring[6] (blue particles).