Laboratoire de Biologie Moléculaire et Cellulaire des Eucaryotes
UMR8226 CNRS/UPMC

MITOFUSION

Mitochondria constitute a real and remarkably dynamic network whose morphology is conditioned by a constant equilibrium between frequent fission and fusion events of their membranes. These processes are essential to shape the ultra-structure of the mitochondrial compartment and are thus also crucial for all mitochondrial functions including oxidative phosphorylation and apoptosis. Consequently, defects in mitochondrial fusion and fission are associated with numerous pathologies and severe neurodegenerative syndromes especially.

While the molecular machineries that promote merging of lipid bilayers are diverse, mitochondria developed a conserved strategy to fuse their membranes, involving proteins that belong to the super-family of Dynamin-Related Proteins (DRPs). DRPs are large GTPases whose GTP cycle is driven by their capacity to auto-oligomerize conferring them with a particular ability to bind and shape the form of biological membranes and especially promote their fission. At the beginning of MITOFUSION, the mechanism by which DRPs can also promote mixing of mitochondrial lipid bilayers remained however poorly understood and represented a tremendous matter of interest.

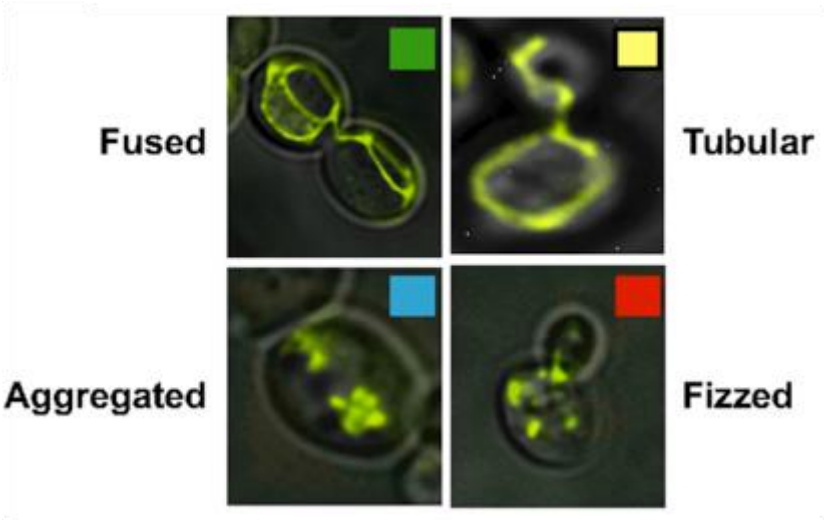
Mitochondria are different from other organelles in that they are composed of two membranes, an outer (OM) and an inner membrane (IM). Fusion of OM and IM is mediated by two distinct DRPs: the mitofusins and OPA1, respectively. Their auto-oligomerization in trans allows for tethering of OM and IM but the mechanistic details of subsequent fusion processes remained unknown. This is despite mutations in both mitofusins and OPA1 being directly implicated in the Charcot-Marie Tooth Type 2A (CMT2A) and Dominant Optic Atrophy (DOA) neurodegenerative syndromes respectively.

Importantly, OPA1 and its yeast ortholog Mgm1 are subject to proteolytic processing resulting in generation of short isoforms that are required for IM fusion to proceed. While such a limited proteolysis has never been demonstrated for mitofusins, mammalian (Mfn1 and Mfn2) and yeast (Fzo1) mitofusins are degraded by the ubiquitin-proteasome system (UPS). In this regard, we have previously shown that ubiquitylation of Fzo1 by the SCFMdm30 ubiquitin ligase and its subsequent degradation by the 26S proteasome take place at the mitochondrial tethering stage and are required for OM fusion to proceed. The precise role of this degradation was nonetheless unknown.

Using the yeast *Saccharomyces cerevisiae* as a model organism, MITOFUSION aimed at dissecting the mechanism by which mitofusins promote mitochondrial tethering and subsequent OM fusion. For this purpose, special emphasis was put on ubiquitin-dependent proteolysis of the yeast mitofusin Fzo1 and a multidisciplinary combination of approaches allying high resolution imaging approaches as well as state of the art biochemistry and cell biology methods were employed.

MITOFUSION assisted the fellow in acquiring a permanent position and establishing his own team. It also transcended the knowledge on how mitofusins catalyze fusion of biological membranes. We expect this will elaborate a molecular basis for better apprehending the physiopathologies associated with mitochondrial fusion but will also provide a mean to compare membrane fusion mechanisms promoted by

other machineries thus generating a more global picture on how mixing of lipid bilayers is accomplished *in vivo*.



Examples of mitochondrial network morphologies seen in the model organism *Saccharomyces cerevisiae*:
Yeast cells expressing mitochondrial matrix targeted GFP (mito-GFP) were visualized by fluorescence microscopy.

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