SOUTENANCE de THESE

Dario de Vecchis

« Gaining insights into mitochondrial membrane fusion through a structural and dynamic atomistic model of the mitofusin Fzo1p "»

Jeudi 26 janvier 2017 à 14h00
Salle de conférences

Mitochondria are dynamic organelles whose morphology is determined by fusion and fission of their membranes. This essential process is known as mitochondrial dynamics. Defects in mitochondrial dynamics are associated with neurological disorders making the investigation of physiological relevance. However, the precise sequence of events that lead mitochondrial dynamics are still not well characterised. Fzo1p, a large GTPase of the Dynamin-Related Proteins superfamily, is a key component in mitochondrial outer membrane fusion in yeast. During this PhD project I built a model of the protein Fzo1p. The structure and dynamics of the model was investigated through molecular modelling and all-atom molecular dynamics simulation in a fully hydrated lipid bilayer environment. The Fzo1p structural model integrates information from several template structures, experimental knowledge, as well as ab initio models of the transmembrane segments. The model is validated experimentally through directed mutagenesis, for instance charge-swap mutations confirm predicted long-distance salt bridges. A series of mutants indicate that coiled-coil domains are required for protein function at variance with its N-terminal region. Overall, the experimental and in silico approaches pinpoint the hinge domains involved in the putative conformational change and identifies critical residues affecting protein stability. Finally, key Fzo1p-GDP interactions provide insights about the molecular mechanism of membrane fusion catalysis. The model provides insight on atomic level and proposes a structure that will be instructional to understanding mitochondrial membrane fusion.