Regulation of Mitochondrial Function/Dysfunction by Focused Ultrasound

I. Research project

The core aim of our research is in the development of a novel approach to unravel the underlying molecular mechanism of how ultrasound (US) influences ion channels activity and leads to regulation of mitochondrial functions/dysfunction. Studies of interactions between US and mitochondria date back to the 1980s [1,2], which basically showed that US may alter mitochondria. However, this research direction received little attention in the following years. Recently, US has become widely used in medical applications, for examples, to open the blood-brain-barrier, to deliver drugs into cells and mitochondria [3].

In recent years, our group has developed ultrasound molecular dynamics (MD) simulation methods to study the interactions between US with various biological systems, including amyloid fibrils, lipid membranes, blood-brain-barrier and liposomes [4-9]. **This COFUND project is particularly aimed at understanding how US influences the molecular structure of the lipid bilayer and of the proteins of the Ca^{2+} ion channels in mitochondria.** The basic idea is illustrated in Fig.1. An ion channel is embedded into a lipid bilayer and irradiated by US. The repetitively compression and expansion of US induce the closing and opening of the channel, leading to the regulation of the ionic currents. As a proof-of-principle approach, we will first focus on the recently determined cryo-electron microscopic structures of the human mitochondrial calcium uniporter (Fig.1). Dr. Nguyen will develop a simulation method that couples regular MD simulation of an ion channel embedded in a lipid bilayer, with external electric force (mimicking electrophysiological recordings) and with an ultrasound. The simulated ionic currents will be calculated and compared directly to electrophysiological measurements. This offers an unprecedented view on the ion permeation process, protein conformational changes and lipid rearrangements at the atomistic scale with the timescale extends from picoseconds to microseconds.

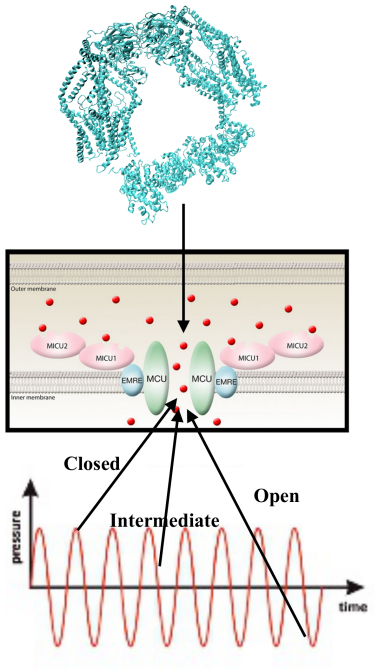

Figure 1. (Upper) The cryo-electron molecular structure of the human mitochondrial calcium uniporter forming ion channels. (Lower) Schematic of the ultrasound regulates the opening , closing and intermediate states of the ion channel.

Our collaborator (Dr. Inserra, LabTAU) will fabricate US transducers operating in the MHz region allows to produce a precise high pressure ultrasound spot at a predetermined location with reduced driving voltage.

In the next steps, we study the molecular mechanisms of ultrasound induced (i) H^+ ion channel, and (ii) assembly/disassembly of proteins forming electron transport chain in mitochondria. This knowledge enable the development of novel non-invasive tools to regulate the function/dysfunction of mitochondria by US. The project is closely connected to the other research axes of the LabEx DYNAMO. For instance, we will study the influence of US on the structure of membrane proteins and their complexes. The nonequilibrium MD simulation developed in this project provides an additional novel approach to the multi-scale integrated structural biology strategy of the LabEX.

II. Responsable scientifique

Dr. Phuong Nguyen is a permanent member of LBT, IBPC.

III. Collaboration

Dr. Claude Inserra is a permanent member of the Laboratory of Therapeutic Applications of Ultrasound (LabTAU, Lyon). LabTAU is a member of the two LabEx CeLyA (Acoustics) and DevWeCan (Cancer), and the Center of Excellence of the Focused UltraSound Foundation. Our collaboration was already granted by a proof-of-concept funding Défi Santé Numérique from the INSERM-CNRS in 2019.

V. References

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