MS39-P05 | STRUCTURAL MECHANISMS GOVERNING REDOX-LINKED PROTON PUMP IN CYTOCHROME C OXIDASE STUDIED BY TIME- RESOLVED X-RAY METHODS

Ghosh, Swagatha (University of Gothenburg, Göteborg, SWE)

Cytochrome c oxidase (CcO) is an integral membrane protein that catalyzes the four-electron reduction of oxygen to water and pumps protons across the inner mitochondrial membrane to establish an electrochemical proton gradient that is used for ATP synthesis. As CcO plays an inevitable role during respiration and defects in CcO functionality are associated with many mitochondrial diseases, the enzyme has been under intense investigation. Crystal structures of CcO have been known for a few decades and these enzymes have been studied with virtually all biophysical and biochemical methods. However, the mechanism and structures of catalytic intermediates during this redox-linked proton translocation still remains elusive. This project aims to elucidate structural mechanisms that couple oxygen- reduction to proton- pumping and gating of proton channel in CcO using time-resolved X-ray methods like wide-angle X-ray scattering (Tr-WAXS) and serial crystallography (Tr-SX). We attempted to study structural changes in *ba_3-type* CcO from *Thermus thermophilus* on binding and photo-dissociation of CO (a mimic of oxygen) and controlled photolysis of a caged- oxygen compound using Tr-WAXS. Moreover, our group has recently determined room temperature structures of oxidized and CO- bound forms of *ba_3-type* CcO from *Thermus thermophilus* using SX. We aim to determine structures of transient intermediates during CcO catalytic cycle with Tr-SX and using CO and caged-oxygen as substrates. These experiments will have major scientific impact on addressing fundamental questions in bioenergetics of cells and possibly provide a guide to develop novel therapeutic agents targeting numerous human mitochondrial diseases.