Special Lecture

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Start Time: Monday, July 24, 2023 04:00 pm

End Time: Monday, July 24, 2023 05:00 pm

Charité – Universitätsmedizin Berlin Fenster der Wissenschaft, Charité Campus Mitte, Charité CrossOver-Gebäude (CCO) Virchowweg 6 10117 Berlin

Can novel structures of 7TM ancestors reveal a missing link to GPCR signaling pathways?

Rhodopsins, a family of evolutionary conserved light-absorbing proteins, are ubiquitous in nature and play key roles in microbial physiology and animal visual perception. Despite having a shared 7TM architecture and utilizing a similar chromophore (retinal) for light sensing, microbial rhodopsins and animal rhodopsins are distinct, and greatly differ in sequence and function; Microbial rhodopsins are a diverse protein family and act as light-activated- sensors, ion pumps and channels, whereas animal rhodopsins are G protein-coupled receptors (GPCRs) that upon illumination trigger G-protein signaling cascades. While the evolutionary relation between those two protein families is unclear, the mere existence of two protein families with similar architecture and a shared cofactor is puzzling and suggests a link between evolved signaling and their 'ancient' ancestors.

In a recent, highly collaborative study, our group discovered and characterized a novel family of rhodopsins in algae – the bestrhodopsins, in which rhodopsins are C-terminally fused to a bestrophin channel. Bestrophins are ion channels, best-known for their involvement in the development of the retinal pigment epithelium in humans and other animals. Cryo-EM analysis of a rhodopsin-rhodopsin-bestrophin fusion reveals a pentameric megacomplex (~700 kDa) with ten rhodopsin units surrounding the channel in the center. Through a serious of structural, biochemical and biophysical characterizations we further show that the rhodopsin components in bestrhodopsins are unusual, and albeit derived from unicellular algae (thus of microbial

origin) have shared properties with animal rhodopsins. We further demonstrate that the domain composition of bestrhodopsins accurately predicts their function as light regulated ion channels, where light sensing through the rhodopsin unit modulates ion permealization in a light depended fashion.

The unique arrangement of the bestrhodopsins that represents both a rhodopsin-heteromer and a rhodopsin-ion-channel fusion within a single protein chain has never been found in nature. The existence of such natural mega-complexes composed of rhodopsin-ion channel fusions is thrilling and poses a wide range of exciting evolutionary and physiological questions that may offer insights into multiple open questions in evolved signaling pathways of GPCRs; these include the functionality of GPCR dimerization, the possibility of direct channel modulation and a potential link in evolution between microbial and animal rhodopsin species. These questions will be discussed here along with providing high resolution snapshots of the bestrhodopsin architecture and their suggested mechanisms of action.

Link to the research group: http://www.weizmann.ac.il/CSB/Shalev-Benami/group-members