SFB 1078

Protonation Dynamics in Protein Function

Mon, **Oct. 28,** 2019

15:15 – 16:15

Freie Universität Berlin
Physics Department
Lecture Hall B

(Arnimallee 14, 14195 Berlin-Dahlem)

Colloquium

Dr. Matthias Elgeti – Jules Stein Eye Institute and Department of Chemistry and Biochemistry, University of California, Los Angeles

Structural underpinnings of biased agonism in G protein coupled receptors

G protein coupled receptors (GPCRs) are important transmembrane signaling proteins which are activated by a multitude of extracellular ligands ranging from small molecules to entire proteins. Active GPCRs couple to different intracellular transducer proteins, such as G proteins and arrestins, thereby triggering diverse cellular responses. A detailed molecular understanding of ligand binding, receptor activation and signal transfer is crucial for the design of receptor-specific and highly efficacious therapeutics with enhanced selectivity ("signal bias") for downstream signaling pathways. EPR distance mapping is uniquely suited in order to investigate the molecular mechanisms underlying GPCR activation and signal transfer to transducer proteins, as it provides access to accurate structural information and a detailed picture of conformational heterogeneity. Using this approach, we performed a comprehensive investigation of the type 1 angiotensin receptor, an important GPCR involved in cardiovascular regulation. We identified four major equilibrium conformations, which are differentially stabilized by ligands in order to achieve distinct signal bias. Comparison with studies on the prototypical, light-sensing GPCR rhodopsin suggests a common structural framework of GPCR biased signaling.

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