Invitation to a RTG 1885 and SFB 1372

# guest talk (hybrid format)

**Thursday, May 5 2022, 5 pm**

Link: https://elearning.uni-oldenburg.de/plugins.php/meetingplugin/room/index/2ead942c1811b3d74521c8481ba470a7/8b838e6b85b7903b7c0332f466b1d01b?cancel_login=1

in presence: W03 1-152 (non RTG&SFB members are kindly asked to participate online, since the seats are limited)


# Daniele Dell`Orco

Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona


## *Synergistic protein-membrane interactions optimize visual sensory transduction*


The enzymatic activity of rhodopsin kinase 1 (GRK1) in photoreceptor cells is crucial for the timely shutoff of the phototransduction cascade through phosphorylation of the G protein-coupled receptor (GPCR) rhodopsin. This process is finely regulated by a Ca2+-dependent feedback mechanism operated by the Ca2+-sensor recoverin (Rec), which prevents the functional interaction between rhodopsin and GRK1 in the dark, when intracellular [Ca2+] in the photoreceptor outer segment is high. The biological function of Rec is achieved by a paradigmatic Ca2+-dependent conformational transition named "myristoyl switch": in the dark-adapted state, the myristoyl moiety covalently bound to the N-terminus is anchored to the disc membrane and Rec binds to GRK1. Upon cell illumination, when Ca2+ drops down to low nanomolar levels, the myristoyl group buries into a hydrophobic cleft, and the protein is thus free to diffuse in the cytosol. The apparent affinity of myristoylated Rec for Ca2+ (Kdapp ~17 mM) is almost two orders of magnitude too low to support the regulation of GRK1 in vivo, since Ca2+ levels in photoreceptor outer segments do not exceed 600 nM.

By applying different spectroscopic analyses, we found that the sole presence of either the target or the disc membrane is not sufficient for Rec to achieve a physiological response to changes in intracellular [Ca2+]. Instead, the simultaneous presence of GRK1 and membrane allows the myristoyl switch to occur in a physiological range of [Ca2+] with high cooperativity, via a conformational selection mechanism. The synergistic interaction of Rec with its target and the disc membrane was also investigated by extensive, unbiased all-atom molecular dynamics (MD) simulations, which proved the spontaneous insertion of the myristoyl group into the membrane for both isolated Rec and for its complex with a peptide from the GRK1 target. The functional membrane anchoring of the myristoyl group was found to be triggered by persistent electrostatic protein-membrane interactions that require specific membrane composition and allosteric interactions. Finally, a comprehensive kinetic model of the phototransduction cascade in rod photoreceptors suggests that this mechanism is crucial for accelerating the shutoff of the signaling cascade in the presence of a light background. This multiscale investigation highlights a paradigmatic example of optimized system, where multi-component interactions may serve to finely regulate the dynamics of GPCR-mediated signaling pathways.