Mechanistic effects of lipids and protein post-translation modifications on signaling over human cell membranes

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Molecular dynamics simulations capable of describing various biological phenomena have become of age recently. This progress was on one hand enabled by intensive work of many scientific groups on development of methodologies and accurate parameters for biomolecular simulations. On the other hand, only the massive parallelization and extensive computational resources facilitated by high-end HPC clusters allow for simulations of sufficient extent (both temporal and spatial) to capture biological processes at the necessary atomistic resolution. The reason therefore is, that in biomolecular simulations accurate interactions and dynamics of millions of particles are estimated at femtosecond timescale while describing processes happening over micro- to milliseconds.

Among the most vivid subjects of interest studied by biomolecular scientists belong molecular mechanisms of signal transmission to the cell interior which has to succeed over the impermeable cell membrane. Here, we have investigated mechanisms by which membrane lipids and protein post-translation modification in concerted fashion modulate the function of G-protein coupled receptors (GPCRs), large and diverse family of proteins responsible for transmembrane signaling in most cellular response events. In detail, we revealed how different patterns of the most common post-translational modification, phosphorylation, modify the interactions between the receptor and membrane lipids. These altered interactions have in turn structural impact on formation of signaling complexes with arrestin.

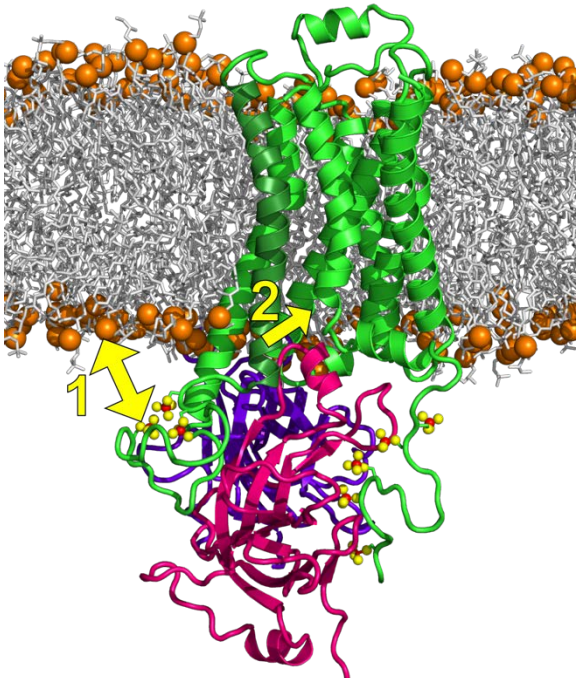

Figure 1: Phosphorylation-dependent release of intracellular loop 3 from the membrane (1) results in locking of arrestin to the receptor (2).

These observations extend our understanding of regulation of transmembrane signaling of G protein coupled receptors, which are already targeted by more than 40% of drugs at the market currently. Every contribution to the understanding of allosteric modulation mechanisms of GPCR signaling is likely to enhance the specificity and efficiency of future drugs, leading to less side effects and optimally to personalized medicine.