UNDERSTANDING G-PROTEIN-COUPLED RECEPTOR DYNAMICS AND FUNCTION BY MEANS OF COMPUTATIONAL STUDIES

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Involvement of G-protein-coupled receptors (GPCRs) in various pathophysiological pathways makes them excellent drug targets as also evidenced by the fact that ca. 40% of currently prescribed medicinal drugs target this receptor family. The interaction network of GPCRs is so complex such that the same receptor can bind to various cytosolic partners to initiate specific signaling pathways. This receptor family has a well-conserved orthosteric ligand binding site making development of target-specific and safer therapeutics challenging. Therefore there is an urgent need for identification of either allosteric sites or alternative signaling partners that can be used for modulation of receptor function. This type of knowledge cannot be achieved solely by experiments, but rather requires contribution from computational studies, in particular, molecular dynamics (MD) simulations which give insight into the time evolution of structural and functional dynamics of the receptor system studied. In this talk, I will present two examples to allosteric modulation of GPCR function.

As to the first example, GPCRs have conserved amphipathic helical motif, namely Helix-8 (Hx-8), which is located just after the seventh transmembrane helix. It is involved in regulation of activation, expression and internalization of the receptor and it bears at least one cysteine residue which can undergo reversible post-translational modification, namely, palmitoylation. We have shown in our *in silico* study that the palmitoylation state of the receptor modulates the membrane insertion depth of Hx-8, and also possibly the C-terminus of the receptor, which acts as a scaffold for both phosphorylation and binding various cytosolic signaling partners. Therefore, the activation of the receptor can be controlled by modulating the accessibility of the C-terminus of the receptor to its cytosolic partners. The likely mechanistic role of Hx-8 has been proved later in an experimental study as well.

As to the second example, GPCR signaling is terminated upon binding of a cytosolic protein, named Arrestin (Arr), to activated-phosphorylated receptor. Recently, this small protein family has gained popularity due to discovery of their roles in initiating G-protein-independent signaling pathways. The members of this family (Arr1, Arr2, Arr3 and Arr4) display differential preference towards the phosphorylation of the receptor. In our study, we have demonstrated a possible mechanism for the source of differential selectivity at the molecular level. This knowledge can be used to regulate Arr binding to receptor under extreme circumstances: for instance, when the receptor

undergoes excessive stimulation and hence down-regulation in the case of congestive heart failure.