Computational Modeling of GPCRS: Insight into the Function of the most Priviledged Drug Targets

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G protein coupled receptors (GPCRs) constitute the largest and most important superfamily of signal transduction membrane proteins known to date. Our study is aimed at understanding, through computational modeling, the molecular mechanisms of GPCR functioning either in their normal conditions or when hit by gain-of-function or loss-of-function mutations. Molecular simulations of the wild type form of luteinizing hormone receptor (LHR) as well as of its spontaneous and engineered mutants were instrumental to infer the structural features, which differentiate the mutation-induced active from the inactive states of this receptor [1]. These features were translated into computational indices instrumental in *in silico* functional screening of novel LHR mutants [1]. Similarly to mutation-induced activation, the interface between the cytosolic extensions of helices 3 and 6 is the target of the structural modifications induced by activating ligands (i.e. agonists). The chemical information transfer from the agonist binding site (on the extracellular side) to the cytosolic domains is mediated by a cluster of aromatic amino acids in helix 6 [1] Computational modeling of the supramolecular organization of GPCRs and their intracellular partners is the current challenge towards a deep understanding of their mechanism of functioning.

[1] Fanelli F., De Benedetti P.G., *Chem. Rev., in press*.

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