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## (I) Single-molecule perspectives of GPCRs

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G protein coupled receptors (GPCRs) form a large family of more than 800 transmembrane proteins that serve as signal transducers between extracellular ligands, such as hormones or medicinal drugs, and intracellular mediators, such as G proteins and arrestins. Recent evidence suggests that, as opposed to the classical two-state model of a single unit switching from an inactive to an active state upon ligand binding, GPCRs exist in a dynamic equilibrium between monomers, dimers and higher oligomers, and monomeric receptors exhibit a high degree of intrinsic structural flexibility.

Applying a slew of single-molecule fluorescence (SMF) methods, we identified and characterized oligomers of the muscarinic M2 receptor and of the attendant Gi protein in vitro, demonstrated their presence in live cells and examined their dynamic, ligand-dependent nature as well as their involvement in cell signalling. Single particle tracking data of receptors and G proteins in live cells shows a broad range of diffusion behaviours, pointing to significant contributions from non-random regimes, in particular for the M2 receptors. Using nanodisc-reconstituted samples of a different GPCR from the same family, the adenosine A2A receptor, we have recently measured nanosecond-to-microsecond conformational dynamics in the receptor. The dynamics was recorded at an intracellular site near the interaction region with the G protein, and it appears to be fine-tuned allosterically by the ligand binding at an extracellular site.

Our results point to a new paradigm for GPCRs functioning as an ensemble of multiple, interchanging active and inactive states, in which different ligands shift not only their populations (conformational selection), but also their intrinsic flexibility (dynamics selection).

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