Structural insights into allostery in GPCRs: G proteins, arrestin and dimers

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GPCRs are dynamic membrane proteins that access a range of conformational states even in the absence of a ligand, with binding of antagonists, agonists or intracellular transducers (e.g. G protein or b-arrestin) biasing the conformation to a subset of states. Binding of agonists to the orthosteric binding pocket affects the conformation of the intracellular surface of the GPCR, that facilitates coupling of a G protein or β-arrestin. In turn, once the transducer has bound, they then affect the orthosteric binding site, which results in increased ligand affinity. Interestingly, ligand affinity with a G protein coupled is not necessarily the same as when β-arrestin is coupled. To understand the molecular basis for these phenomena, we compared structures of the β_1-adrenoceptor in the inactive state with that bound to a G protein mimetic (nanobody), with the same ligand bound in both states. The results clearly demonstrate an increase in the number of ligand receptor contacts and/or number/strength of hydrogen bonds, that is consistent with increased ligand affinity when a G protein is coupled [1]. A cryo-EM structure of the β_1-adrenoceptor coupled to β-arrestin identified subtle changes in the orthosteric binding site compared to when a G protein mimetic is coupled, consistent with weaker ligand binding [2].

In the second half of my talk I will discuss the potential for allosteric communication across the dimer interface in the yeast receptor Ste2 [3, 4]. We determined five cryo-EM structures of Ste2 either in the ligand-free state, bound to antagonist, bound to the agonist α-factor (two structures) or to agonist and G protein. In all these states, Ste2 is a homodimer, with the interface formed primarily from transmembrane helix H1 and a domain-swapped N-terminus. Intriguingly, there appears to be allosteric cross-talk between the two protomers across the dimer interface in active states, but not active states.

1. Warne, T, Edwards, PC Doré, AS, Leslie, AGW, Tate, CG (2019) Molecular basis for high-affinity agonist binding in GPCRs. Science **364**, 775-778
2. Lee, Y. *et al.* (2020) Molecular basis of β-arrestin coupling to formoterol-bound β_1-adrenoceptor. Nature **583**, 862-866
3. Velazhahan, V., Ma, N., Pándy-Szekeres, G., Kooistra, A.J., Lee, Y., Gloriam, D.E., Vaidehi, N. & **Tate**, C.G. (2021) *Dimeric structure of the Class D GPCR Ste2 coupled to two G proteins*. Nature **589**, 148-153
4. Velazhahan, V., Ma, N., Vaidehi, N. & **Tate**, C.G. (2022) *Activation mechanism of the class D fungal GPCR dimer Ste2*. Nature **603**, 743-748