Ligands identification and Structural studies of several aGPCRs

As one of the evolutionarily ancient families in GPCR superfamily, aGPCRs have been found to serve as crucial molecular switches in regulating many physiological and pathophysiological processes, including brain development, angiogenesis, inflammation, mechano-sensing, ion-water homeostasis, and cell fate determination (Nat Rev Drug Discov 2019, 869-884; NEJM, 2016, 374, 656-663, Science 2018, 361, 6403). A notable feature of almost all aGPCR family members is the presence of large extracellular regions harboring the GPCR autoproteolysis-inducing (GAIN) domain, which often undergoes intramolecular self-cleavage to produce α and β subunits. Distinct from the activation mechanisms of all other GPCR families, tethered agonism by inserting Stachel-like sequences within the seven-transmembrane (7TM) bundle has been proposed based on biochemical analysis and lies at the heart of aGPCR signalling and function. Although the physiological functions of aGPCRs as well as their mutations related to human diseases have been emerging recently, the structural understanding of aGPCRs are still challenging.

Recently, we identified that aGPCR are the membrane receptors of a series of steroid hormones by screening data and cell-based reporter assays. Many steroid hormones elicit quick physiological responses through nuclear-receptor independent pathways, which might be through engagement with unknown membrane receptors; however, the corresponding membrane receptors for these steroid hormones remain elusive. We identified that (1) GPR97 is the endogenous membrane receptor of the glucocorticoids and we solved the cryo-EM structure of beclomethasone-bound GPR97 in complex with heterotrimeric Go, which provide important insights into how steroid hormones activate an aGPCR (***Nature. 2021;589(7843):620-626***); (2) GPR126 and GPR64 as the membrane receptors of progesterone and dehydroepiandrosterone (DHEA), respectively, and revealed the mechanism of adhesion GPCRs paring with different endogenous steroid hormones (***PNAS. 2022;119:e2117004119; Nat Chem Biol. 2022***); (3) determined the cryo-EM structures of GPR133β-Gs, GPR114β-Gs, GPR64β-Gs and GPR112β-Gs complexes, and elucidated the tethered activation mechanisms of aGPCR members which underlies the mechano-force sensing by these receptors (***Nature. 2022,604(7907):763-770; Nature. 2022. 604(7907):771-778.***).