The role of protein dynamics in G protein coupled receptor activation

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G protein coupled receptors (GPCRs) conduct the majority of transmembrane responses to hormones and neurotransmitters and mediate the senses of sight, smell and taste. Thanks to advances in protein engineering, crystallography and cryo-electron microscopy (cryoEM) over the past 14 years there are now more than 500 deposited high-resolution structures of GPCRs including inactive states, active states and GPCR-G protein complexes. These structures have provided important insights into common mechanisms of G protein activation for Family A and Family B GPCRs. However, they don't fully explain the complex behavior of many GPCRs that signal through more than one G protein isoform, and through G protein independent pathways. Moreover, we still do not fully understand the mechanism of G protein coupling specificity. This complex functional behavior provides evidence for the existence of multiple functionally distinct conformational states that may be too transient or unstable to be captured by crystallography or cryoEM. We have used fluorescence, EPR and NMR spectroscopy to study the dynamic properties of several GPCRs. I will discuss a few examples of what these studies have taught us about the role of protein dynamics in GPCR signaling.