Signaling across the plasma membrane and into cells via GPCRs and Ras

DEPARTMENT OF CHEMISTRY & CHEMICAL BIOLOGY

G protein-coupled receptors (GPCRs) are important signaling molecules in higher organisms. Strategically located at the cellular periphery, these membrane proteins transmit extracellular information into the cell. The human genome contains over 800 GPCRs, which have evolved to bind thousands of different chemicals and instigate a wide array of cellular responses. As such, GPCRs are targeted by 30% of drugs and play central roles in appetite, mood, blood pressure, and pain control. However, it is unclear how receptors achieve robust signaling from active states that appear to be short-lived. To resolve this apparent contradiction, I will show how signaling can be regulated by specific interactions between receptors and lipids from their native environment. I will also show how free energy landscapes underling protein-protein interactions and folding upon binding can be used to predict the interactions between GPCRs and downstream signaling proteins. The final section of this talk will focus on pathological signaling from Ras proteins, which harbor activating mutations in 20% of all cancers. In theory, the signaling output from overactive Ras mutants can be decreased by small molecules whose binding stabilizes inactive states or blocks interaction with downstream effectors. However, decades of research have failed to produce drugs that directly target Ras. Therefore, I will present preliminary efforts in a new line of attack: the rational design of compounds that can rescue Ras'ability to deactivate itself via catalysis.

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