Structural Insight Into G Protein Coupling And Activation Of Human Frizzled Receptors

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G protein-coupled receptors (GPCRs) are membrane proteins that function by coupling with intracellular transducer proteins known as G proteins. Frizzled (FZD) receptors, classified under class F, are a unique family of GPCRs. These receptors are crucial for various biological processes, and dysregulation in their function can lead to diseases, including cancer.

The lipid environment within the phospholipid bilayer significantly impacts the structure and function of GPCRs. The phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) in particular, is crucial for activation and signalling of many GPCRs, including FZD receptors. However, the mechanism of how lipids regulate GPCRs is not completely understood.

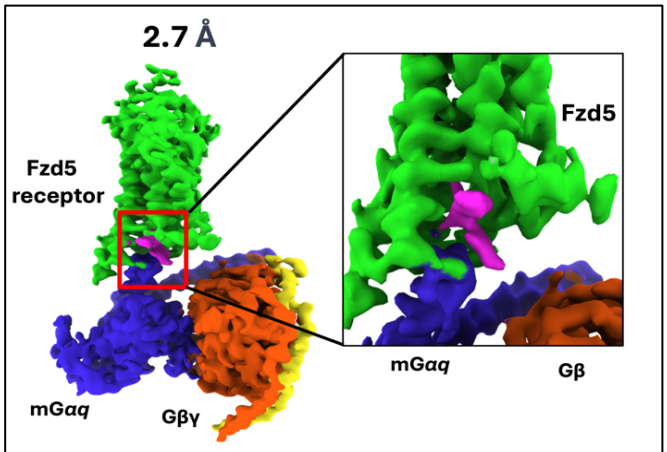

Figure: Cryo-EM structure analysis of FZD7--mGq-Gβγ complex. (A) electron density map of the complex with coloured components (FZD7 receptor, mGs, Gb, Gy and unique density as green, blue, orange, yellow, magenta respectively) (B) zoomed view of the binding site between FZD7 and mGaq.

We have used cryo-electron microscopy to determine the high-resolution structures of FZD5-mGq (2.7 Å) and the FZD7-mGs (2.6 Å) complexes. These structures revealed previously unobserved density at the receptor-G protein interaction site, which we hypothesized to be a lipid. This hypothesis is supported by preliminary lipidomic mass spectrometry data showing significant enrichment of various lipids in purified FZD-G protein complexes compared to membrane preparations without FZD receptors. However, the exact identity of the density present in our structures is still unknown. Future research will focus on identifying these lipids and understanding their role in FZD receptor activation and signal transmission. This information will reveal new mechanisms of FZD regulation and open novel avenues for therapeutic intervention.