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Drosophila GoLoco-protein Pins as a target of Gαo-mediated G protein coupled receptor signaling

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Heterotrimeric G-proteins are molecular switches that regulate numerous aspects of cellular physiology by transducing the signals from G protein-coupled receptors (GPCRs). In the basal state, the Gα-subunits of the heterotrimeric G proteins are GDP-liganded (the inactive form) and bind to the βγ-complex. GPCRs can activate guanine nucleotide exchange on the Gα-subunits to produce the active, GTP-bound state. GoLoco domains present in many proteins play important roles in multiple heterotrimeric G protein-dependent activities, physically binding the Gα-subunits of the Gαi/o class. In most cases GoLoco binds exclusively to the GDP-loaded form of the Gα-subunits. Our biochemical and genetic experiments as well as structural modeling show that the poly-GoLoco protein Pins binds to both the GDP- and GTP-forms of *Drosophila* Gαo. We identify the Pins GoLoco domain 1 as necessary and sufficient for the unusual interaction with Gαo-GTP. We further pinpoint the central Lysine residue present in this domain as responsible for the interaction. Molecular modeling suggests that the side chain of this Lysine points directly into the guanine nucleotide-binding pocket of Gαo, stabilizing the extra negative charges of the γ-phosphate group of GTP. Such a positively charged amino acid is unique in the *Drosophila* GoLoco proteome, but is conserved in several GoLoco domains of other organisms. We conclude that Pins, through its GoLoco domain 1, is a target for Gαo-mediated GPCR signaling.