Abstract

Deciphering structural design principles for interaction specificity in G protein signaling

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For cellular signaling cascades to function correctly, their protein components must recognize their appropriate partners accurately. This requirement presents a challenge for living cells, as related components are used repeatedly in both parallel and intersecting cascades within the same cell. Signaling therefore requires that the interactions of particular protein-family members be tailored to each signaling cascade via interaction specificity. Such design principles also govern the interaction specificity between Regulators of G protein Signaling (RGS) proteins and heterotrimeric G proteins. We investigate these principles using a combination of structure-based energy calculations and experimental measurements. Our results show that effective interactions can be set by different combinations of positive design elements that enhance interactions, while specificity is mainly set by “disruptor residues” that attenuate interactions and thereby function as negative design elements. Redesign of these interfaces and experimental validation reveals a multi-tiered specificity system that combines positive and negative design elements to modulate RGS-Gα interactions in a specific fashion.