Structure of Adenylyl Cyclase 5 in Complex with Gβγ Offers Insights into *ADCY5*-Related Dyskinesia

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Abstract

The nine different membrane-anchored adenylyl cyclase isoforms (AC1-9) in mammals are stimulated by the heterotrimeric G protein $G\alpha_s$, but their response to Gβγ regulation is isoform-specific. For example, AC5 is conditionally activated by Gβγ. Here, we report the 7 Å cryo-EM structures of ligand-free AC5 in complex with Gβγ and of a dimeric form of AC5 that could be involved in its regulation. Gβγ binds to a coiled-coil domain that links the AC transmembrane region to its catalytic core as well as to a region that is known to be a hub for isoform-specific regulation. We confirmed the Gβγ interaction using both purified proteins and cell-based assays. The interface with Gβγ involves AC5 residues that are the sites of gain-of-function mutations in humans suffering from dyskinesia, indicating that the observed interaction is important for motor function. A molecular mechanism wherein Gβγ either prevents dimerization of AC5 or allosterically modulates the coiled-coil domain, and hence the catalytic core, is proposed. Because our mechanistic understanding of how individual AC isoforms are uniquely regulated is limited, studies such as this may provide new avenues for isoform-specific drug development.