Colloquia in Cellular Signaling

Venue: Medical University Vienna, Center for Physiology and Pharmacology, Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "**Leseraum**".
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Structural basis of nucleotidyl cyclase dimerization

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Abstract:

Nucleotidyl cyclases, including membrane-integral and soluble adenylyl and guanylyl cyclases are central components in a wide range of signalling pathways. These proteins are architecturally diverse, yet many of them share a conserved feature, a helical region that precedes the catalytic cyclase domain. The role of this region in cyclase dimerization has been a subject of debate. Although mutations within this region in various cyclases have been linked to genetic diseases, the molecular details of their effects on the enzymes remain unknown. I will discuss my group's first results in this field, and will present an X-ray structure of the cytosolic portion of the membrane-integral adenylyl cyclase Cya from Mycobacterium intracellulare in a nucleotide-bound state. The helical domains of each Cya monomer form a tight hairpin, bringing the two catalytic domains into an active dimerized state. Mutations in helical domain of Cya mimic the disease-related mutations in human proteins, recapitulating the profiles of the corresponding mutated enzymes, adenylyl cyclase-5 and retinal guanylyl cyclase-1. Our experiments with full-length Cya and its cytosolic domain link the mutations to protein stability, and ability to induce an active dimeric conformation of the catalytic domains. The high degree of sequence conservation indicates that this domain is an integral part of cyclase machinery across protein families and species. Our structural, biochemical and biophysical experiments provide a framework for understanding the role of the helical domain and explain the effects of the disease-associated mutations in the corresponding regions of human adenylyl and guanylyl cyclases.