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Oral presentation

Structural and mechanistic insights into cGMP signaling

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Background

The second messenger cGMP plays a central role in regulating bodily functions, e.g. in the cardiovascular and nervous systems. cGMP is formed by guanylyl cyclases (GC), activates target proteins, and is finally hydrolyzed by cyclic nucleotide phosphodiesterases (PDE). PDEs and GCs are widely used as drug targets, spurring interest in mechanistic and structural insights into their regulation.

Different to the closely GC-related Class III adenylyl cyclases, until recently no structures of eukaryotic GCs could be obtained and all bacterial Class III proteins were found to be ACs rather than GCs. For PDEs, in contrast, a wealth of structures of their catalytic domains is available. However, first structures of regulatory GAF domains present in several PDEs gave contradictory results on their assembly and function, so that further structural data are needed for a complete understanding.

Results

We could show that the cyanobacterial Class III cyclase Cya2 shows high specificity for GTP versus ATP, revealing it to be the first bacterial GC [1]. We solved the crystal structure of Cya2, providing first structural insights into the universal GC family. Structure and mutagenesis studies show that a conserved glutamate, assisted by an interacting lysine, dominates substrate selection by forming hydrogen bonds to the substrate base. We find, however, that a second residue involved in substrate selection has an unexpected sterical role in GCs. Further structural differences and kinetic data indicate the molecular basis of substrate recognition and sensitivity to non-competitive cyclase inhibitors [2], giving hints for the development of specific GC inhibitors.

We further solved the crystal structure of the central GAF domain of a mammalian PDE5 (manuscript in preparation). The dimerization mode of the isolated domain indicates how the holoenzyme dimer is assembled, and the hydrohpbic interaction interface suggests a model for the mechanism of activation of PDE5 through ligand binding to the neighbouring GAF domain.

Conclusion

We could identify Cya2 as the first bacterial GC, and sequence similarity searches suggest that GCs are also present in other bacteria. Structural and biochemical data on this model system for mammalian GCs indicate mechanisms for substrate binding and recognition and for inhibitor sensitivity, giving hints for the development of GC-specific inhibitors. Our structural data on the PDE5 GAF domain further indicate a model for PDE5 assembly and activation, increasing our understanding of this element within the cyclic nucleotide signalling system and helping further drug development efforts against this target.

References

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