7 Summary

The universal *second messenger* cAMP plays a key role in the mammalian intracellular signal transduction. It controls a variety of pivotal cell functions ranging from cell growth and differentiation to transcriptional regulation and apoptosis. The key step in the regulation of cAMP is the exact cell/tissue-specific modulation of those enzymes that synthesize cAMP: the adenylyl cyclases (ACs). Particular mammalian ACs are represented by at least nine different isoforms (ACI-ACIX). All isoforms are susceptible to the stimulatory α-subunit of heterotrimeric G proteins ($G\alpha_s$), besides that each AC is uniquely regulated by multiple signals from G proteins, calcium and kinases. Due to their competency as detectors and integrators of coincident regulatory signals they form intersection points for the cross-talk of different signaling pathways. Thereby, the regulatory hot spots on the AC molecules represent ideal targets to selectively modulate branches of bifurcated cascades without affecting the complete receptor-triggered signaling network. Up to now little is known about the detailed mechanisms underlying the isoform-specific regulation of ACs. In the present study molecular insights in the isoform-specific stimulation of ACII by Gβγ and ACI by calcium/calmodulin (Ca/CaM) were yielded.

For the first time we have identified motifs on an AC enzyme that could be proven to be necessary for the Gβγ-regulatory effect:

(1) the PFAHL-motif localized on the variable C1b-domain of ACII,

(2) the KF-loop localized on the catalytic C2a-domain of ACII.

Apart from the data regarding isoform ACII, a new Gβγ-regulatory pathway was discovered for isoform ACIII: The ACIII is directly inhibited by Gβγ *in vitro*.

In terms of the stimulation of isoform ACI by Ca/CaM there was already one regulatory motif known: the AC28-region localized on the variable C1b-domain of ACI. In the present work we have figured out that:

(1) the C1b-domain is not sufficient for the ACI-stimulation by Ca/CaM,

(2) the catalytic C2a-domain of ACI is also crucial for the ACI-stimulation by Ca/CaM. We have identified the VLG-motif on this domain and provided evidence for a direct interaction between Ca/CaM and this sequence.

The data presented here reveal that the regulatory signal transfer is based on more than one molecular interface between regulator and effector. Different roles of the regulatory motifs as signal transfer regions or general binding domains are discussed.