Structure of the Pseudokinase Domain of CASK

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Kinases are one of the largest enzyme families. About 10 % of all kinase domains encoded in the human genome are pseudokinases, i.e. they are catalytically inactive. However, the exact mechanisms of their inactivation remain unknown. CASK, an adaptor molecule at the synapses, harbors a catalytically inactive CaM-kinase domain that is homologous to Ca^{2+}/calmodulin-dependent protein kinases. Using data collected at the BW6 beamline of DORIS, we have solved the structure of the CASK CaM-kinase domain in two crystal forms. The protein maintains an active kinase fold. Equivalents of all functional elements known from active kinases can be located in the structures (Figure 1). However, the selectivity of the nucleotide binding pocket is apparently compromised, since the protein can bind either 5'-ATP or 3'-AMP (Figure 1). We are presently investigating the structural basis for inactivation.

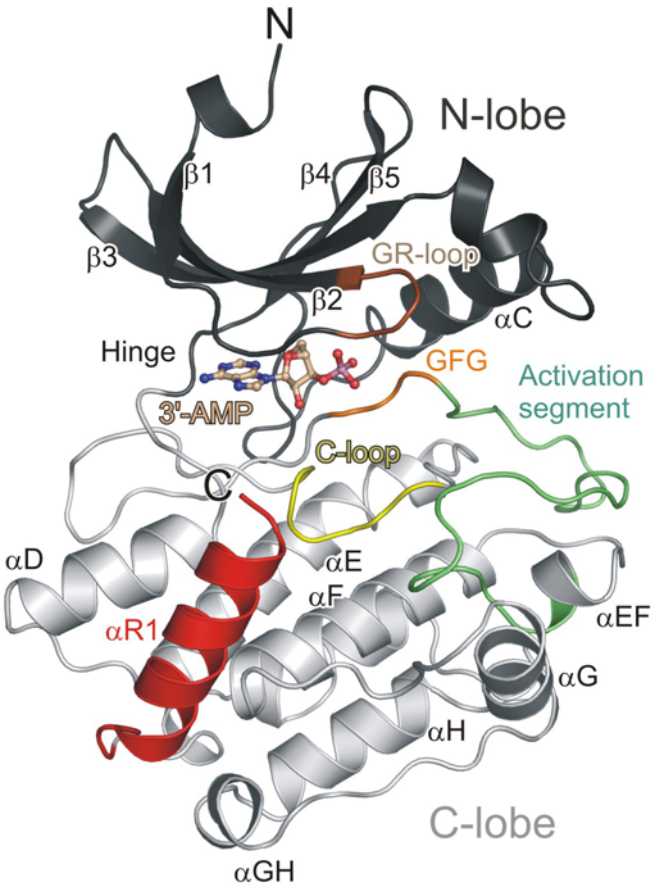

Figure 1: CaM-kinase domain of CASK. GR-loop - glycine-rich loop; C-loop - catalytic loop.