Structural insights for activation of retinal guanylate cyclase by GCAP1

GCAP1, a member of the neuronal calcium sensor (NCS) subclass of the calmodulin superfamily, confers Ca\(^{2+}\)-sensitive activation of retinal guanylyl cyclase 1 (RetGC1). I will present NMR resonance assignments, residual dipolar coupling (RDC) data, functional analysis, and a structural model of GCAP1 mutant (GCAP1\(^V77E\)) in the Ca\(^{2+}\)-free/Mg\(^{2+}\)-bound activator state. NMR chemical shifts and RDC data reveal Ca\(^{2+}\)-dependent differences for residues 170-174. An NMR-derived model of GCAP1\(^V77E\) contains Mg\(^{2+}\) bound at EF2, and looks similar to Ca\(^{2+}\) saturated GCAP1 (RMSD=2.0 Å). Ca\(^{2+}\)-dependent structural differences occur in the fourth EF-hand (EF4) and adjacent helical region (residues 164-174 called the Ca\(^{2+}\)-switch helix). Ca\(^{2+}\)-induced shortening of the Ca\(^{2+}\)-switch helix changes solvent accessibility of T171 and L174 that affects the domain interface. Although the Ca\(^{2+}\)-switch helix is not part of the RetGC1 binding site, insertion of an extra Gly residue between S173 and L174 as well as deletion of R172, S173 or L174, all caused a decrease in Ca\(^{2+}\)-binding affinity and abolished RetGC1 activation. We conclude that Ca\(^{2+}\)-dependent conformational changes in the Ca\(^{2+}\) switch helix are important for activating RetGC1, and provide further support for a Ca\(^{2+}\) myristoyl tug mechanism.

Biography

James B Ames has completed his PhD in Chemistry department from University of California, Berkeley and Post-doctoral studies from Stanford University School of Medicine. He is currently a Professor in the Chemistry department. He has published more than 100 papers in reputed journals and has been serving as an Editorial Board Member of Nature Scientific Reports and Frontiers in Molecular Neuroscience.

jbames@ucdavis.edu