Vision Research Seminar Series

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Guanylyl Cyclase Activating Proteins: Calcium-Magnesium Sensors In Phototransduction And Congenital Retinal Dystrophy

Guanylyl cyclase activating proteins (GCAP) are recoverin-like proteins within a broader family of EF-hand neuronal calcium sensors. GCAPs are essential components of calcium feedback and they play the key role in shaping photoresponses and adaptation of rods and cones by accelerating their recovery from hyperpolarization. The function of GCAPs is defined by their ability to activate photoreceptor membrane guanylyl cyclase (retGC), when cGMP-gated channels become closed after illumination and the free calcium concentrations drop. The activation of retGC in the light compensates for the hydrolysis of cyclic GMP and accelerates re-opening cyclic GMP-gated channels and thus facilitates the recovery. In the dark, when cGMP hydrolysis stops and free calcium concentrations rise to their resting level, GCAPs bind calcium and return retGC back to its inactive state. GCAPs are not just calcium-, but rather calcium/magnesium-binding EF-hand proteins, and binding of magnesium is also essential for their function as retGC regulators. The transition from the activator to the inhibitor form of GCAPs occurs as a result of Mg^{2+} being replaced by Ca^{2+} ions, and while the switching between the activator and the inhibitor form itself requires binding of calcium, it is also their affinity for magnesium that determines the actual range for the calcium-sensitivity of retGC regulation. Only at physiological intracellular concentration of magnesium the dynamic range for retGC regulation by GCAPs falls within the physiological range of the intracellular free calcium (in mammals, between 25 nM in the light and 250 nM in the dark). GCAPs have four EF-hand domains, but only three of them are capable of binding Ca^{2+} and/or Mg^{2+} - the N-terminal EF-hand domain in the course of evolution lost its ability to bind calcium and instead became a part of the target enzyme recognition domain. Mutations found in GCAPs associate with congenital dominant cone and rod dystrophies in human patients that result in blindness. When replicated in transgenic mouse models, one of these mutations, Y99C, decreases GCAP1 affinity for calcium, causes deregulation of retGC in the retina, increases free intracellular calcium concentrations in photoreceptors, and results in their degeneration. The Y99C mice lose their ERG responses, and the progressive loss of the rod/cone ERG accompanies the rod/cone apoptosis, however, individual photoreceptors remain active until their death, with their single photon response amplitude and kinetics changed consistently with the free cGMP increase. Mutations in retGC related to human cone-rod dystrophy also result in shifting calcium sensitivity of retGC1 via change in the relative affinity of retGC for the activator versus the inhibitor form of GCAPs.

Wednesday, February 9, 2005
4:00 p.m.
1220 MRB III

(Refreshments prior to seminar)
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