# Structural and evolutionary analysis of the activation mechanism in the SK channel-Calmodulin complex

***by Brittany Montesino | Jessica Siltberg-Liberles***

*Abstract Id:* ***484*** *Submitted:* ***March 5, 2019*** *Event:* ***Conference for Undergraduate Research at FIU 2019***
*Topic:* ***Biology***

SK-channels (SKs) are small-conductance calcium-activated potassium channels that are involved in the hyperpolarization of neurons and other excitable cells. Calmodulin, a calcium-sensing protein, is complexed with SK. Upon calcium-binding, calmodulin undergoes a conformational change that is propagated to the SK channel. Ultimately, the channel opens, allowing potassium through. The human genome encodes four different SK-channels (SK1-4). Although the SK family has been associated with various effects on the brain and heart, the activation mechanism has remained elusive. A CryoEM study conveying human SK4 bound to calmodulin in three different conformations (when calcium is not bound, the first bound state, and the active state when potassium can pass through) was recently published. By analyzing these conformations, we mapped the interface residues involved in the conformational changes leading to the activation of the SK4 channel. This information was combined with an examination of the molecular evolution of this complex across vertebrates to elucidate the conservation of the activation mechanism for the four SK clades and their interactions with calmodulin in the different conformations. It was found there are more radical changes at the channel-calmodulin interface than within the channel. This suggests that once activation by calmodulin has been achieved, the mechanism is conserved. While current SK channel antagonists mostly target the common channel pore, these clade-specific sites which target the substitutions at the interface with calmodulin present opportunities to develop more specific SK-channel blockers. These blockers can be used as potential drug targets for ailments such as hypertension and Parkinson’s.