Understanding calcium-activated chloride channels in health and disease

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Ca^{2+}-activated Cl^- (Cl_{Ca}) channels are small conductance anion channels activated by a rise in intracellular Ca^{2+} concentration. Cl_{Ca} channels have multiple important roles in cellular physiology, including epithelial secretion of electrolytes and water, regulation of vascular smooth muscle tone, sensory transduction (pain, smell, temperature), generation of rhythmic slow waves for gut motility, neuronal and cardiac excitability.

My lab is particularly interested in the roles of Cl_{Ca} channels in cardiac excitability, first described in the early 1990's in atrial, ventricular and Purkinje cells isolated from several species. During the cardiac action potential Cl_{Ca} currents are activated in response to Ca^{2+} entry *via* voltage-gated Ca^{2+} channels and Ca^{2+} release from intracellular sarcoplasmic reticulum (SR) stores. Under physiological conditions, Cl_{Ca} currents are expected to carry a significant amount of transient outward current and participate in the early repolarization process. During pathological Ca^{2+}-overload, activation of Cl_{Ca} currents can contribute to the arrhythmogenic transient inward current.

Despite the fact that Cl_{Ca} channels are implicated in diverse cellular processes, our understanding these channels has been limited by the fact that, for many years, their molecular identity remained unknown. Bestrophins and anoctamins are two families of membrane proteins that function as Cl_{Ca} channels and are the subject of research activity in my lab. Our group has made strides to provide a complete characterization of the electrical properties of recombinant bestrophin channel genes isolated from heart. We provided evidence that expression of bestrophin channels results in macroscopic chloride currents that are sensitive to physiological levels of intracellular Ca^{2+} (EC_{50}; 175 nM Ca^{2+}) and that bestrophin Cl_{Ca} channels are present at the membrane of cardiac myocytes. More recently, biochemical studies identified that bestrophin-3 channel (Best3) physically interacts with histidine rich calcium-binding protein (Hrc), a key regulator of sarcoplasmic reticulum (SR) Ca^{2+}-uptake, storage and release. This direct coupling of Best3 with Hrc suggests that Best3 channels in addition to mediating Cl_{Ca} currents at the plasma membrane may also function as an intracellular Cl_{Ca} counterion channel, balancing charge movement across the SR membrane during Ca^{2+} release and reuptake.

Anoctamin 1 (Ano1) Cl_{Ca} channel belongs to a family of membrane proteins and has been linked to essential physiological roles in a variety of excitable cells. Our molecular studies in heart identified that Ano1 transcripts undergo complex alternative splicing to create channel diversity. We determined that Ano1 Cl_{Ca} channels are clustered at the intercalated discs of cardiac myocytes, were they demonstrate strong co-localization with connexin-43 (Cx43) gap junction protein. A direct interaction between Ano1 channels and Cx43 was verified in co-immunoprecipitation studies. These findings indicate that Ano1 in its reported function as a Cl_{Ca} channel plays a role in cell-cell communication in this excitable membrane domain. In summary, the identification of anoctamins and bestrophins as molecular components of Cl_{Ca} channels has been fundamental for our understanding of the functions of Cl_{Ca} channels. Defining the cellular distribution and localization of these channels and unraveling the mechanisms of Cl_{Ca} channel regulation by Ca^{2+} are areas that will provide further insight to their physiological functions and pathological roles in human diseases.