LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

International Summer School Practice

Computational Modeling of the Role of Connexin43 Hemichannels in the Formation of Cardiac Arrhythmias

Connexin43 (Cx43) is the primary connexin expressed in human ventricles. Under normal physiological conditions, Cx43 is localized at the longitudinal ends of cardiomyocytes within intercalated discs, where it forms functional gap junction channels. Gap junction channels are composed of two connexin hemichannels from adjacent cells that dock head-to-head, creating low-resistance pathways for direct intercellular ion permeation. Under various pathological cardiac states, Cx43 becomes lateralized to the non-junctional sarcolemma, forming unapposed hemichannels that connect the cell cytoplasm directly with the extracellular space.

Due to their large pore diameter, the prolonged opening of even a small number of hemichannels can lead to significant disturbances in cytosolic ion homeostasis and cellular electrical stability. The resulting changes in resting membrane potential and cytosolic ion gradients (in particular, intracellular Na^+ accumulation and Ca^{2+} overload) can alter the function of other ionic currents, pumps, and exchangers, leading to abnormalities in cardiac action potential propagation and aberrant Ca^{2+} release from the sarcoplasmic reticulum.

To investigate these complex interactions, we will employ computational modeling – an increasingly vital approach for formulating testable hypotheses and performing initial screening of potential therapeutic targets. Because there are currently no approved clinical therapeutics specifically targeting Cx43 hemichannels directly, searching for secondary or co-targeted ionic channels offers a promising alternative strategy. We will combine biophysical models of Cx43 hemichannels developed in our laboratory at the Institute of Cardiology with established cell-level models of cardiac excitation-contraction coupling. Computer simulations will be applied to evaluate the interactions between Cx43 hemichannel activity and other ionic currents, helping to identify potential pharmaceutical targets to mitigate the harmful effects of pathological Cx43 hemichannel activation.