CBR

The Centre for Blood Research Seminar Series

Wednesday, December 3rd, 2014

LSC 3 - Life Sciences Centre

2350 Health Sciences Mall

12-1pm

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UBC

"Cardiac arrhythmias, epilepsy, and muscle disorders: Mutations in Sodium channels and Ryanodine Receptors at high resolution"

The electrical activity of neurons and cardiac tissue is governed by ion channels. Mutations in these channels can result in severe genetic conditions, collectively known as 'channelopathies'. Our lab studies the molecular mechanisms that regulate the ability of ion channels to gate, and we focus on two types of channels that are selective for calcium or sodium ions.

1) Voltage-gated sodium channels are involved in shaping the action potential in many excitable cells, and mutations have been linked to Long-QT and Brugada syndromes, congenital epilepsy, and much more. A large number of these mutations are found in a region that confers calcium-sensitivity to the sodium channel. Through the use of high-resolution crystal structures and electrophysiological assays, we find that the disease-causing mutations affect this calcium-sensing ability.

2) Ryanodine Receptors are large calcium-selective ion channels primarily found in the Sarcoplasmic Reticulum. Over 500 mutations have been linked to stress-induced arrhythmias, muscle weakness, and malignant hyperthermia. Through solving crystal structures of various domains, we have been able to map these mutations and analyze their effect on the structure and stability of the protein. We propose a mechanism whereby a disease hot spot dampens channel activity, and disease-causing mutations facilitate channel opening.