Filip Van Petegem performed his undergraduate and PhD studies at Ghent University, Belgium. There he was trained as a structural biologist, solving crystal structures of extremophilic enzymes in the lab of Jozef Van Beeumen. This work allowed him to peer into the adaptation mechanisms of enzymes to extreme cold and hot temperatures. In 2002 he joined the laboratory of Daniel Minor at UCSF for postdoctoral work on ion channels. There he produced the first high-resolution structures of voltage-gated calcium channel domains. By combining X-ray crystallography with electrophysiology, he was able to help decipher the mechanisms through which beta subunits and calmodulin regulate this complex membrane protein. He joined the Department of Biochemistry and Molecular Biology at UBC in july 2007, where he received tenure in 2012. His research program focuses on understanding the mechanisms of ion channels in native and diseased states. A major theme in his lab includes the Ryanodine Receptor, a 2.2MDa calcium release channel located in the ER and SR, and his lab has been able to decipher several allosteric mechanisms of this membrane protein giant. Another theme includes voltage-gated sodium channels, proteins that carry the upstroke of action potentials in excitable cells. His lab has been funded by the CIHR, the Human Frontiers in Science Program, and the Heart and Stroke Foundation of Canada.

Abstract

Regulation of Voltage-Gated Sodium Channels by Calcium Ions and Auxiliary Subunits

Voltage-gated sodium channels are integral membrane proteins that can rapidly depolarize the plasma membrane. They are responsible for the action potential in many excitable cells, including neurons and cardiac myocytes. The cardiac sodium channels are targets for a multitude of mutations that cause Long-QT and Brugada syndromes, two types of inhereted arrhythmias. They consists of two subunits: a pore-forming alpha-subunit, which forms the ion conduction pathway, and an auxiliary beta-subunit, which can have profound effects on protein expression, pharmacology, and electrophysiological properties. Sodium channels undergo very complex regulatory events, and have the property to inactivate, a process whereby channel activity is shut down. The rapid inactivation is mediated by distinct cytosolic components that form hot spots for disease-causing mutations. Here we describe high-resolution crystal structures of the auxiliary subunits, and of the inactivation machinery. Coupled with electrophysiological assays, we describe mechanisms that can regulate channel inactivation, and the mechanisms through which disease-associated mutations can affect channel function.