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Structural insights into cholesterol regulation of inwardly-rectifying K+ channels

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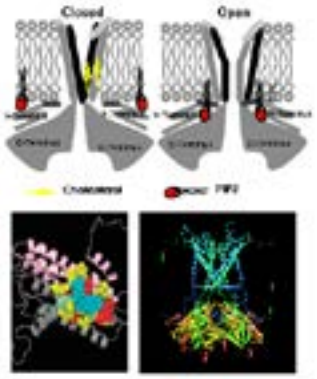
Cholesterol is known to play a significant role in regulating the function of multiple membrane proteins including a growing number of ion channels. Our studies focus on inwardly-rectifying K+ (Kir) channels that are ubiquitously expressed in mammalian cells and are known to play key role in membrane excitability and shear stress sensation. In this study, we have shown that Kir channels are suppressed by loading the cells with cholesterol and enhanced by cholesterol depletion. A series of studies revealed that cholesterol interacts with the channels directly by stabilizing them in a long-lived closed "silent" state and that multiple structural features of the channels are essential for conferring their cholesterol sensitivity. Using a combined computational-experimental approach, we show that cholesterol may bind to two non-annular regions that form hydrophobic pockets between the transmembrane helices of the adjacent subunits of the channel. The location of the binding regions suggests that, cholesterol modulates channel function by affecting the hinging motion at the centre of the pore-lining transmembrane helix that underlies channel gating. In addition, we identified a series of residues in the C and N-terminus of the channel. These are critical for conferring cholesterol sensitivity to the channels, but are not part of the binding sites. These residues form a distinct cytosolic structure, a cholesterol sensitivity belt which surrounds the cytosolic pore of the channel in proximity to the transmembrane (TM) domain, and includes residues whose mutation results in abrogation of the channel's cholesterol sensitivity. Further analysis identified a reversal residue chain comprised of residues that link one of the cholesterol sensitivity belt residues with a distant cytosolic residue that constitute a two-way molecular switch of the channel sensitivity to cholesterol. Further studies are needed to elucidate the connection between cholesterol binding and channel.



Biography

Irena Levitan has completed her PhD and is a Professor of Medicine and Adjunct Professor of Bioengineering at the University of Illinois at Chicago. Her current research focuses on cholesterol regulation of ion channels and cellular biomechanics. Her group has provided the first comprehensive structural insights into cholesterol regulation of K+ channels and the cross-talk between cholesterol and other regulators of these channels. She was named a Guyton Distinguished Lecturer by the Association Chairs of Departments of Physiology for her quantitative and biophysical work on cholesterol modulation of ion channels and how this can affect integrated organ function. She is an author of more than 70 publications and a leading Editor of *Cholesterol Regulation of Ion Channels and Receptors* (Wiley, 2012) and *Vascular Ion Channels in Physiology and Disease* (Springer, 2016).

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