Scientific Meeting
AuPS | ASB
HOBART · 2022

AUSTRALIAN SOCIETY FOR BIOPHYSICS

Abstract: 171P

The mechanism and structural basis of ion conduction in an inward rectifier potassium channel

Ruitao Jin[1], Sitong He[1], Jacqui Gulbis[2,3], Brian Smith[1]

1. *La Trobe Institute for Molecular Science, La Trobe University, Melbourne, VIC, 3086, Australia*
2. *Structural Biology Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, 3052, Australia*
3. *Department of Medical Biology, The University of Melbourne, Parkville, VIC, 3052, Australia*

K^+ channels are transmembrane pores which allow K^+ to diffuse across cell membranes. To control ion flux, they need to switch between conducting and non-conducting states by a process of gating. The canonical gating mechanism proposes the channel is closed by a constriction in the conduction pathway, opened by a conformational change sufficiently large to accommodate a fully hydrated ion to pass. However, no structural evidence has been forth coming that captures the open conformation. In this study, molecular dynamics simulations are conducted to investigate the gating mechanism for ion permeation through the prokaryotic KirBac3.1 channel. Using enhanced sampling methods, the free energy profiles suggest the energy barrier for a potassium ion passing the constriction is negligible and not sufficient to impede ion flux. The energy barrier at the narrow collar is comparable to the wild type even when locking the channel in the assumed closed conformation by constraining the collar. Partial dehydration of the K^+ with only three or four water molecules surrounding the ion while passing through the collar is observed, inconsistent with the premise of the canonical model that only K^+ with a complete hydration shell can be conducted. These simulations confirm that the constriction at bundle crossing region that had become folklore to be the gating element in the canonical model is ineffective in controlling channel conduction. Further MD simulations discover a limiting energetic barrier within the conduction pathway formed at another hydrophobic constriction site. This constriction is gated by fatty acyl tails of lipids within the fenestrations in the channel walls by engaging the sidechains of the residues forming that constriction, revealing an interactive relationship between the channel and bound phospholipids is the foundation of channel gating. Together, with experimental evidence from collaborators, we present a new gating and regulation mechanism of Kir channels.