# 柳振峰团队解析 TRIC 通道结构与门控机制

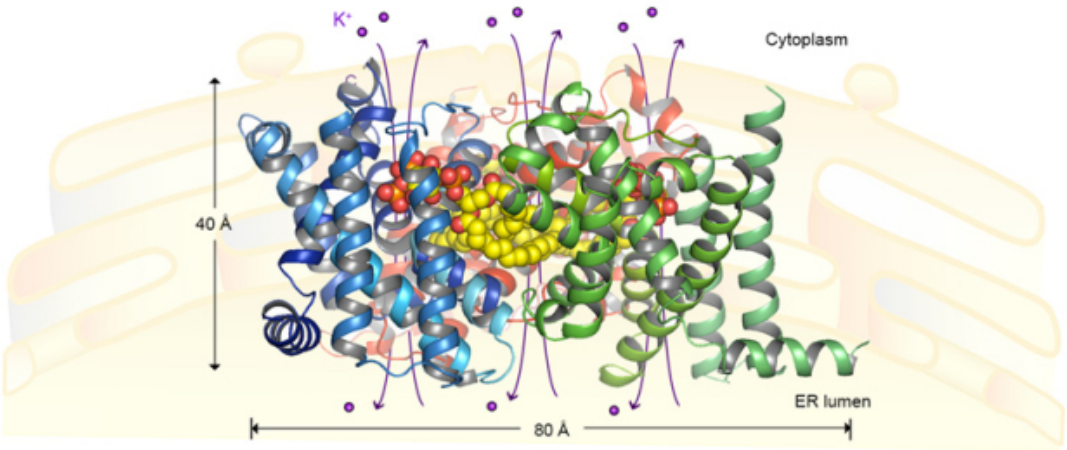
# Zhenfeng Liu Reported the Pore Architecture of TRIC Channels and Insights into Their Gating Mechanism

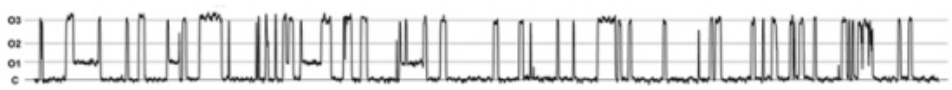
【Nature 系列】10 月 27 日，Nature 期刊在线发表了中国科学院生物物理研究所柳振峰课题组关于三聚态胞内阳离子通道（TRimeric Intracellular Cation channel, TRIC channel）的结构与门控机制研究成果。

近年来，TRIC 通道被发现是一种位于肌质网或内质网（SR/ER）膜上的单价阳离子通道，它们主要通过通透钾离子或钠离子来促进 SR/ER 腔内的钙离子向胞浆释放。编码 TRIC 通道蛋白的基因遗传缺失或突变会导致高血压、心脏病、呼吸缺陷和脆骨病。

TRIC 通道分子水平的三维结构与门控机制多年来一直是个谜。柳振峰课题组率先解析了秀丽线虫（Caenorhabditis elegans）来源的 TRIC-B（CeTRIC-B）通道的两个不同构象态的晶体结构。此次所报道的研究工作中首次发现了 TRIC-B 通道蛋白能够特异性地结合内源性的磷脂酰肌醇 4,5-二磷酸（PIP2）脂类分子，并形成了稳定的同源三聚体复合物。每个单体中各含有一个可通透 K+离子等单价阳离子的不对称孔道，其结构特征与经典的四聚态 K+离子通道截然不同。内源性的 PIP2 分子介导了 TRIC 通道的三聚化，同时直接参与孔道结构的形成，并与推测的电压感应基序以及钙离子结合区有相互作用。这一发现揭示了 PIP2 分子在胞内离子通道中所起的关键作用，也拓展了人们对于 PIP2 与离子通道相互作用关系的认识。胞质侧的钙离子对于 TRIC 通道的活化有促进作用，研究结果发现 TRIC-B 通道在结合钙离子前后发生了局部结构的变化，并基于此提出了该通道活化过程的机理模型，对其开放时的门控机制做出了预测。

新型胞内离子通道是潜在的药物作用靶点，相关研究有望促进新药的开发，该领域的研究工作近年来开始引人关注。此次所完成的 TRIC 通道结构机理方面的研究结果，将为深入开展与胞内钙信号动态调控有关的生理过程、病理以及药理的分子基础研究提供全新的视角。




# Pore architecture of TRIC channels and insights into their gating mechanism

# TRIC 的孔结构和它们的门控机制

中国科学院生物物理研究所 柳振峰

2016 年 10 月 27 日
doi:10.1038/nature19767

Abstract

Intracellular $Ca^{2+}$ signalling processes are fundamental to muscle contraction, neurotransmitter release, cell growth and apoptosis. Release of $Ca^{2+}$ from the intracellular stores is supported by a series of ion channels in sarcoplasmic or endoplasmic reticulum (SR/ER). Among them, two isoforms of the trimeric intracellular cation (TRIC) channel family, named TRIC-A and TRIC-B, modulate the release of $Ca^{2+}$ through the ryanodine receptor or inositol triphosphate receptor, and maintain the homeostasis of ions within SR/ER lumen. Genetic ablations or mutations of TRIC channels are associated with hypertension, heart disease, respiratory defects and brittle bone disease. Despite the pivotal function of TRIC channels in $Ca^{2+}$ signalling, their pore architectures and gating mechanisms remain unknown. Here we present the structures of TRIC-B1 and TRIC-B2 channels from *Caenorhabditis elegans* in complex with endogenous phosphatidylinositol-4,5-biphosphate (PtdIns(4,5)$P_2$, also known as $PIP_2$) lipid molecules. The TRIC-B1/B2 proteins and $PIP_2$ assemble into a symmetrical homotrimeric complex. Each monomer contains an hourglass-shaped hydrophilic pore contained within a seven-transmembrane-helix domain. Structural and functional analyses unravel the central role of $PIP_2$ in stabilizing the cytoplasmic gate of the ion permeation pathway and reveal a marked $Ca^{2+}$-induced conformational change in a cytoplasmic loop above the gate. A mechanistic model has been proposed to account for the complex gating mechanism of TRIC channels.