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YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"Channelopathy and regulation of TRPM3 channels"

by
Siyuan Zhao

Molecular Biology, Genetics, and Cancer Program

BSc, 2014, Nanchang University, Jiangxi, China
MSc, 2016, Georgetown University, Washington DC, US

Thesis Advisor: Tibor Rohacs, Ph.D., M.D.
Professor
Department of Pharmacology, Physiology & Neuroscience

Tuesday, November 29th, 2022
1:30 PM
Medical Science Building (MSB): H609B

Join Zoom Presentation:
https://rutgers.zoom.us/j/91204731091?pwd=bk05a3FhZmhYYlNYK09rektSbXdQUT09

Meeting ID: 912 0473 1091
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ABSTRACT

The Transient Receptor Potential Melastatin 3 (TRPM3) ion channel is a non-selective calcium permeable ion channel, and it belongs to the Transient Receptor Potential (TRP) superfamily. TRPM3 is a thermosensitive nociceptor channel, which can be activated by heat. TRPM3 knockout mice show impairment in avoiding noxious heat and have defects in developing inflammatory heat hyperalgesia. TRPM3 can also be activated by endogenous neurosteroid pregnenolone sulfate (PregS), and synthetic compounds such as CIM0216 and clotrimazole.

The presence of *de novo* substitutions of TRPM3 has been reported in patients with intellectual disability and epilepsy in 2019. Either TRPM3 mutation Val 990 (992) Met or Pro 1090 (1092) Gln was found in those patients. My research indicates that both mutations make the channel overactive but possibly through two distinct mechanisms. Even though both mutations increase the sensitivity of TRPM3 towards agonists and heat activation, TRPM3-Val990Mel preferentially makes the channel more sensitive towards agonists such as PregS and CIM0216 whereas the Pro1090Gln mutation increases the sensitivity of TRPM3 towards heat activation predominantly. Both mutated TRPM3 channels can be inhibited by the TRPM3 inhibitor primidone, which is a clinically approved anti-epileptic drug, suggesting the potential treatment of this type of disease.

Since TRPM3 channels are crucial for many physiological processes including heat sensation, my research also focused on the regulation of TRPM3. Phosphatidylinositol 4,5-biphosphate [PI(4,5)P2] is a minor component of the cell membrane but its presence is required for the activation of many ion channels including TRPM3. My research has proposed several putative PI(4,5)P2 binding residues in TRPM3 channels, mutating which increased the sensitivity of TRPM3 to the inhibition mediated by PI(4,5)P2 depletion . The activity of TRPM3 can also be regulated by G protein coupled receptors (GPCRs). My research confirms that the direct binding between Gβγ proteins and TRPM3 inhibits the channel activity. We also identified and functionally characterized the binding residues in the Gβ subunit. Additionally, the interaction between PI(4,5)P2 regulation and Gβγ regulation of TRPM3 channels is proposed in this project.