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"Phosphatidic acid is an endogenous negative regulator of PIEZO2 channels and mechanical sensitivity"

By

Matthew Gabrielle
Cell Biology, Neuroscience, and Physiology Ph.D. Program

B.S. Roger Williams University, Bristol, RI - 2019

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Friday, December 6th, 2024
1:00 P.M.
MSB B619

Join Zoom Presentation:
https://rutgers.zoom.us/j/98924468725?pwd=yLrI5SS1g4xqqhsTdJVmLKCMgMM25b.1

Meeting ID: 989 2446 8725
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Abstract

Mechanically-activated PIEZO2 channels expressed in peripheral sensory neurons of the dorsal root ganglia (DRG) are critical for sensing touch, proprioception and inflammatory mechanical allodynia. While PIEZO2 channels play an important role in mechanosensation, relatively little is known about other proteins regulating their activity. In this study, we investigate the influence of TMEM120A (TACAN), previously proposed as a high-threshold mechanically-activated ion channel in nociceptive DRG neurons. Our findings reveal that co-expression of TMEM120A decreases the amplitude of mechanically-activated PIEZO2 currents and increases their activation threshold, while not affecting PIEZO1 or TREK1 channels. Importantly, TMEM120A did not produce mechanically-activated currents on its own. Notably, *Tmem120a* and *Piezo2* expression overlap in mouse DRG neurons, and siRNA-mediated knockdown of *Tmem120a* enhances PIEZO2 currents and lowers their activation threshold, supporting TMEM120A as a negative modulator of PIEZO2 activity. Furthermore, TMEM120A expression elevates cellular levels of phosphatidic acid and lysophosphatidic acid (LPA), aligning with its structural resemblance to lipid-modifying enzymes. Both intracellular application of phosphatidic acid and LPA, as well as prolonged exposure to the nonhydrolyzable analog carbacyclic phosphatidic acid (ccPA), selectively inhibit PIEZO2 without affecting PIEZO1. Optogenetic activation of phospholipase D (PLD), which generates phosphatidic acid, also inhibits PIEZO2. Conversely, PLD inhibition increases PIEZO2 activity and enhances mechanical sensitivity in behavioral experiments in mice. Collectively, these findings reveal lipid regulators and the PLD pathway as significant modulators of PIEZO2 activity, highlighting potential targets for selective inhibition.