BIOCHEMISTRY 640

(Biomembranes Discussion Group)

Wednesday, December 6, 2017

Room 4-70 Medical Sciences Building

4:00 PM

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"PIP2 controls magnesium gatekeeper TRPM6 activity"

Mg2+ homeostasis is regulated by a variety of hormonal and pathological conditions. Mg2+ deficiency has been implicated in many diseases, ranging from neurological to cardiovascular diseases. TRPM6, as a gatekeeper of human Mg2+ homeostasis, has been demonstrated to be regulated at expression levels by hormones such as estrogen and AngII, metabolic acidosis/alkalosis, immunosuppressant tacrolimus, diuretics Thiazide, and EGF. Since TRPM6 is crucial for human Mg2+ homeostasis, patients carrying TRPM6 mutations develop hypomagnesemia and secondary hypocalcemia (HSH). However, the activation mechanism of TRPM6 has remained unknown.

The authors demonstrate that phosphatidylinositol-4,5-bisphophate (PIP2) controls TRPM6 activation and Mg2+ influx. Stimulation of PLC-coupled M1-receptors to deplete PIP2 potently inactivates TRPM6. Translocation of over-expressed 5-phosphatase to cell membrane to specifically hydrolyze PIP2 also completely inhibits TRPM6. Moreover, depolarization-induced-activation of the voltage-sensitive-phosphatase (Ci-VSP) simultaneously depletes PIP2 and inhibits TRPM6. PLC-activation induced PIP2-depletion not only inhibits TRPM6, but also abolishes TRPM6-mediated Mg2+ influx. Furthermore, neutralization of basic residues in the TRP domain leads to nonfunctional or dysfunctional mutants with reduced activity by PIP2, suggesting that they are likely to participate in interactions with PIP2. These data indicate that PIP2 is required for TRPM6 channel function; hydrolysis of PIP2 by PLC-coupled hormones/agonists may constitute an important pathway for TRPM6 gating, and perhaps Mg2+ homeostasis.Understanding the critical role of PIP2 in TRPM6 channel function may facilitate our understanding of how Mg2+ contributes to physiological/pathological processes, as well as the development of therapeutic approaches for hypomagnesemia treatment