SL15 Amazing TRP Channels: Entering the Age of TRPpathies

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The *T*ransient *R*eceptor *P*otential (TRP) superfamily comprises now 28 mammalian cation channels which are subdivided into six subfamilies: TRPC ('Canonical'), TRPV ('Vanilloid'), TRPM ('Melastatin'), TRPP ('Polycystin'), TRPML ('Mucolipin') and the TRPA ('Ankyrin') groups. For all these TRP channels, the enormous diversity of gating mechanisms and permeation properties will be shortly reviewed. In general, TRP channels play a unique role as cell sensors, are involved in a plethora of Ca^{2+}-mediated cell functions, and play a role as "gate-keepers" in many homeostatic processes such as Ca^{2+} and Mg^{2+} reabsorption.

As a special example, two TRP channels, TRPM4 and TRPV4, will be discussed, which show a surprising gating promiscuity. TRPM4 is a Ca^{2+} activated channel which is strongly modulated by phosphatidylinositol-phosphates (PIP_2). Knocking down of this channel induces a mast-cell phenotype characterized by an increased allergic sensitivity. TRPM4 deficient mice develop heart hypertrophy and hypertension. TRPM5 plays a role in insuline release. A diabetes type 2 like phenotype will be described in *trpm5-/- mice.* TRPV4 is activated by mechanical stimuli, heat, and α-phorbols. The first endogenous activators of this channel include arachidonic acid and epoxyeicosatrienoic acids. TRPV4 is expressed and is functional in the urothelium of mouse bladder. Observation of the voiding pattern showed incontinence-like disturbances in *trpv4*$^{-/-}$ mice and an atypical cystometric pattern indicating that this phenotype is due to a dysfunction of a mechano-sensor in urothelium affecting stretch-induced release of ATP. In addition, *trpv4-/-* mice develop a "mild" vascular phenotype with a decreased endothelium dependent vasorelaxation and a mild bone phenotype, which is related to an osteoclast dysfunction. TRPV4 is required for the final differentiation of osteoclasts. Therefore, *trpv4 deficient* mice develop an increased bone mass and do not develop, when unloaded, osteoporis as wild type mice. Finally, a new TRPV4 bone channelopathy, an autosomal recessive brachyolmia, caused by a gain-of-function mutations of TRPV4 will be described.

Selected Reviews

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