Channels 8:4, 285–285; July/August 2014; © 2014 Landes Bioscience

Channels News & Views

Klotho: A new trafficking modifier of Kv7.1/KCNE1 channels

Comment on: Almilaji A, Pakladok T, Muñoz C, Elvira B, Sopjani M, Lang F. Upregulation of KCNQ1/KCNE1 K(+) channels by Klotho. Channels (Austin) 2014; 8:8; PMID:24457979; http://dx.doi.org/10.4161/chan.27662

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The Klotho gene codes for a type-I membrane protein that exists in two forms—as a transmembrane protein and as a secreted protein. Particularly the secreted form of Klotho suppresses oxidative stress and growth factor signaling and regulates ion channels and transporters. It was reported that Klotho overexpression suppresses insulin/IGF-1 signaling. This signaling pathway was indicated as a central switch in determining life span. Overexpression of Klotho was shown to extend life span and polymorphisms in functional Klotho (KL-VS variant) seem to be associated with "*healthy aging*".[1] Klotho seems to be involved in chronic kidney disease—mineral and bone disorder, chronic kidney disease and an associated increased cardiovascular risk in patients. Underlying these clinical incidents is a complex endocrine cross-talk along the so called "*FGF23-Klotho axis*" among kidneys, parathyroid gland, intestine and bones. The associated cardiovascular incidents include left ventricular hypertrophy, vascular calcification, hearing impairment and arrhythmias.[2]

In the current issue of Channels Almilaji et al. report the regulation of Kv7.1/KCNE1 channel complexes.[3] Alternative names of Kv7.1 are KCNQ1 or KvLQT1 and for KCNE1 mink or IsK respectively. Voltage-gated Kv7.1 channels allow for fast and K^+ selective rapid passage of potassium ions through cellular membranes. Kv7.1 channels regulate diverse physiological processes such as ion coupled transport, hormone secretion, vesicle cycling, cell motility, development and cell excitability. Functional impairment of Kv7.1 causes aspects of channelopathies and thus present a primary therapeutic target for diseases such as cardiac arrhythmias, hearing defects, diarrhea and diabetes.[4] Kv7.1 channels form heteromeric channels with regulatory β-subunit KCNE1 to allow for the cardiac delayed rectifier repolarizing current I_{Ks}.[5,6] The surface density of Kv7.1/KCNE1 channels was reported to be controlled by specific trafficking events of channel containing membrane vesicles. In particular, ER export, endocytosis and recycling are events that determine Kv7.1/KCNE1 plasma density.[7,8] Almilaji et al. report that Klotho associated β-glucuronidase acivity influences Kv7.1/KCNE1 channel density. Currently the precise cellular mechanism is elusive. As trafficking of several membrane proteins like TRPV5 and NaPi cotransporter are regulated by Klotho a common mechanism may be under control of Klotho. It will thus be very insightful to learn what this interesting effect is based on.

The functional regulation of Kv7.1/KCNE1 channels by Klotho may be of significant relevance: An astonishing similarity of effects due to functional impairment of Kv7.1/KCNE1 and Klotho like hearing impairment, kidney and intestinal effects and arrhythmias allow for speculations: Could the Kv7.1/KCNE1 channel be one central mediator of physiological Klotho functions. In this case altered Klotho function may cause a complex pathophysiological condition with aspects of a channelopathy. The study by Almilaji et al. sets the starting point to future experimentations that will shed light on important questions relevant to basic science and human health.

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