Evolutionary divergence and conservation of TRPA1 channels

A large body of evidence has established the Transient Receptor Potential Ankyrin 1 ion channel (TRPA1) as a promising drug target for pain, itch and respiratory diseases. Despite the progress, whether TRPA1 is a receptor for noxious cold has been a lasting debate, as cold activation of the channel has been reported by several groups but disputed by others. Here we attribute the controversy to species difference. We show that that mouse and rat TRPA1 is activated by cold, but human or rhesus monkey TRPA1 is not activated by either cold or heat under the same conditions. The species-specific cold activation is determined by a single residue difference in the S5 transmembrane domain. Additionally, TRPA1 from invertebrates and ancestral vertebrates (e.g., fly, mosquito, frog and snakes) are activated by heat, as reported by several groups. Therefore TRPA1 exhibits a spectrum of temperature sensitivity, from heat-sensitive, cold-sensitive to temperature-insensitive. The thermal divergence of TRPA1 is in direct contrast to its sensitivity to electrophilic compounds, which is conserved during animal evolution.

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