detection system we found that AQP2 is critical for the release of ATP induced by TRPV4activation. This ATP release occurs by an exocytic and a conductive route. ATPe, in turn, stimulates purinergic receptors leading to ATPe-induced ATP release by a Ca 2+ -dependent mechanism. Finally, we found that the addition of ATP eliminates the differences previously reported in the migration of RCCD 1 cells, depending on the expression of AQP2. The increased migration of AQP2-RCCD 1 is likely related to the ability to modulate the levels of Ca 2+ and ATP in microdomains close to the focal adhesions. Elucidating the joint function of AQPs with TRPs channels is essential to improve our understanding of mammalian physiology in health and disease.

CELL DAMAGE AND APOPTOSIS INDUCED BY TRPV4 ACTIVATION IN HUMAN MELANOMA CELLS AND HACAT KERATINOCYTES

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The transient receptor potential channels subtype 4, TRPV4 channels, are calcium-permeable cation channels that are activated by a broad variety of physicochemical stimuli. TRPV4 channels have been suggested to serve as physiological osmosensors, mechanosensors, thermosensors, and implicated also in epithelial/endothelial barrier functions in several tissues, such as arteries, lungs, kidneys, and skin. TRPV4 are promising drug targets to treat disease, like bladder dysfunction, sepsis, and pulmonary edema caused by heart failure, giving rise to novel selective small molecule modulators, such as the activator, GSK1016790A, and several selective inhibitors, such as HC067047. Whether TRPV4 were also mechanistically implicated in melanoma cell proliferation was not clear. Here, we hypothesized that TRPV4 is expressed in human melanoma and that pharmacological activation interferes with cell proliferation. TRPV4 functions were studied in melanoma cell lines (A375, SK-MEL-28, MKTBR), immortalized non-cancer keratinocytes (HaCaT), and murine 3T3 fibroblasts by patch-clamp, qRT-PCR, optical mapping of intracellular calcium measurements, cell proliferation, and flow cytometric assays of apoptosis and cell cycle. GSK1016790A elicited TRPV4 currents in all cell lines. GSK1016790A-induced currents were blocked by HC067047. TRPV4 mRNA expression was demonstrated by qRT-PCR. In A375 cells, TRPV4 activation was frequently paralleled by co-activation of calcium/calmodulin-regulated KCa3.1 channels. Light microscopy showed that TRPV4-activation produced rapid cellular disarrangement, nuclear densification, and detachment of a large fraction of all melanoma cell lines and HaCaT cells. TRPV4-activation induced apoptosis and drastically inhibited A375 and HaCaT proliferation that could be partially prevented by HC067047. Our study showed that human melanoma cell lines expressed functional TRPV4 channels and that the TRPV4-activator, GSK1016790A, caused a strong calcium-overload and cellular disarrangement, increased the rate of apoptosis, and strongly inhibited cell proliferation/survival. Similarly, GSK1016790A induced apoptosis and impeded proliferation of HaCaT keratinocytes, a spontaneously immortalized aneuploid keratinocyte cell line from human skin. Pharmacological targeting of TRPV4 could be an alternative or adjuvant therapeutic strategy to treat melanoma progression and other proliferative skin disorders.

STRUCTURE-BASED VIRTUAL SCREENING IDENTIFIES NOVOBIOCIN, MONTELUKAST, AND CINNARIZINE AS TRPV1 MODULATORS WITH ANTICONVULSANT ACTIVITY IN-VIVO.

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Epilepsy is a disease characterized by the recurrent presence of seizures. It affects more than 50 million people worldwide. Pharmacotherapy is the first-line treatment for this pathology. However, approximately 30% of patients do not respond to existing pharmacological therapies. Transient Receptor Potential Vanilloid 1 (TRPV1) is a nonselective cation channel modulated by ligands, pH, temperature, and voltage. It has been proposed as