TRPV4 is downregulated in keratinocytes in non-melanocitic human skin cancer

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The pleiotropic family of transient receptor potential (TRP) channels is largely distributed in tissues and organs (Nilius et al., 2007). A subgroup of channels, which include the TRP vanilloid 1 (TRPV1), TRPV2, TRPV3, TRPV4, the TRP melastatin 8 (TRPM8) and the TRP ankyrin 1 (TRPA1) is particularly expressed in somatosensory neurons in the skin, where they sense changes in temperature (thermo-TRP) and a large variety of endogenous and exogenous stimuli. Expression these thermo-TRPs is, however, not confined to sensory nerve fibres, as they have been found in numerous non-neuronal cutaneous cell types, including some cutaneous cells. TRP channels exhibit also differential expression in cancer tissues and may exert potential tumorigenic role (Duncan et al., 2001).

However, expression and function of TRP channels in skin cancers has been poorly investigated. Here, we studied the distribution and level of expression of thermo-TRPs, in human normal skin and in a series of premalignant and invasive cutaneous carcinomas, collectively referred to as non-melanoma skin cancers (NMSCs) (Weinstock et al., 1994. These include basal cell carcinomas (BCCs) and squamous-cell carcinomas (SCCs). Immunohistochemistry analysis were used for channel identification, and cytokine release was used for studying their function. Expression of TRPV1, TRPV2, TRPV3 and TRPA1 was localized in basal and suprabasal epidermal keratinocytes, and was observed in adnexal structures (Radtke et al., 2011; Sokabe et al., 2010). No change in their expression was found across the various tumors.

However, the marked expression of TRPV4 was practically abrogated in keratinocytes of NMSCs compared to normal skin. A series of pro-inflammatory cytokines, including interleukin-8 (IL-8) were shown to down-regulate TRPV4. We showed that TRPV4 in keratinocytes was downregulated by cell exposure to a variety of pro-inflammatory cytokines. Finally, interleukin-8 (IL-8), which contributes to TRPV4 downregulation, is released upon TRPV4 activation in keratinocytes.The ability of TRPV4 activation in keratynocytes to release IL-8 underline the possibility of pro-tumorigenic agents to downregulate the channel in a autocrine fashion. Present findings suggest that TRPV4 downregulation may represent an additional diagnostic marker and a major pathogentic factor in NMSCs. However, this hypotheses should be confirmed in larger studies.