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Keratinocyte Growth Regulation TRP-ed Up Over Downregulated TRPV4?

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Abstract

This commentary on an exciting new study (Fusi et al., 2014) puts the finding of TRPV4 downregulation in several nonmelanoma skin cancers into context. The original paper points toward possible use of TRPV4 as dermatopathologic marker, also toward the possibility that downregulated TRPV4 can affect biological properties of the cancer, by enhancing, but also regulating tumor growth. As calcium-permeable TRPV4 has recently been identified as UVB-receptor in skin keratinocytes, where it regulates skin tissue injury and pain after UVB overexposure, it is discussed whether TRPV4 downregulation can also be found in other non-UVB-exposed cancers.

In this issue of *JID*, an exciting new study by Daniela Massi's and Romina Nassini's groups at the University of Florence, Italy, shows that keratinocytes from precancerous lesions and from malignant skin cancers exhibit considerable downregulation of TRPV4 ion channels (Fusi et al., 2014). Because sweat glands and endothelial cells function as endogenous positive controls, their finding suggests that TRPV4 immunolabeling could be a novel tissue marker in several skin cancers and could improve diagnostic accuracy in dermatopathology. However, the approach's specificity needs to be confirmed by examining additional controls such as proliferative noninflammatory lesions (e.g., seborrheic keratosis and verruca vulgaris), as well as healthy skin proximal to cancer. Such a broad study would also allow investigators to correlate clinical features of a cancer with the extent of TRPV4 downregulation.

Relevance for other epithelial tumors with TRPV4 expression in the epithelium before tumorigenesis

The question arises whether TRPV4 downregulation is restricted to skin cancer, whereas other cancers, in which TRPV4 shows physiological epithelial expression, might not share

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CONFLICT OF INTEREST

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this regulation. If this were so, then epidermis-specific TRPV4 downregulation in neoplastic (or hyperproliferative) epithelia might be associated with UVB exposure. Skin is often UVB exposed, but intra-oral, esophageal, and colonic epithelia—all of which express TRPV4—are not. In other words, does TRPV4 downregulation in epithelia selectively affect UVB carcinogenesis? Moreover, is TRPV4 downregulation in skin cancer ultimately caused by UVB exposure? Chronically UVB-damaged epidermis will be relevant, where initial studies have demonstrated TRPV4 upregulation (Moore et al., 2013).

Does downregulation of the UV receptor, TRPV4, protect UVB-exposed keratinocytes against calcium overexposure—or is it only an epiphenomenon?

We can now consider whether in keratinocytes UVB exposure and downregulation of expression of a channel that is activated by UVB—TRPV4 (Moore et al., 2013)—are linked in an autoregulatory feedback loop. TRPV4 downregulation would protect the cell against an overabundance of calcium, and, in the context of UVB exposure, against (detrimental) consequences of UVB-mediated inflammation (including neurogenic inflammation) and tissue injury. However, because keratinocytes' TRPV4 expression normally facilitates calcium influx, which is also known to sustain the layered architecture of the epidermis by regulating keratinocyte proliferation and differentiation (Yuspa et al., 1989), TRPV4 downregulation may represent cause, effect, or coincidence. First, TRPV4 downregulation might enable dedifferentiation and uncontrolled growth of keratinocytes, thus leading to a malignant phenotype. Alternatively, it may be a regulatory response of malignantly transformed cells. We can entertain the concept that TRPV4 downregulation is a counter-regulatory mechanism of the malignantly transformed cell because the stratified architecture of cancerous epithelia has been lost, and calcium influx would fuel growth, migration, and metastasis of (pre) cancerous cells. Finally, it may be an epiphenomenon without critical relevance for the biological properties of the lesion. The scientific community is now positioned to probe into these questions.

Cellular events prompting downregulation of TRPV4 expression in epithelia vs. regulation in the opposite direction in primary sensory neurons

Fusi et al. (2014) show that IL-8 and other pro-inflammatory cytokines lead to TRPV4 downregulation in HaCaT cells: a transformed human keratinocyte cell line with resemblance to keratinocyte cancer cells. Chen et al. (2013) have uncovered the opposite regulation of TRPV4 in inflammatory trigeminal pain. In temporo-mandibular joint inflammation there is upregulation of TRPV4 in trigeminal ganglion neurons. In the paper by Moore et al. (2013), we noticed TRPV4 upregulation in response to acute UVB-mediated injury, which was also apparent in chronic UVB photodermatitis. These observations raise the following question: at what point, coinciding with which event during epidermal carcinogenesis, will TRPV4 be downregulated in keratinocytes and by which gene-regulatory mechanism(s)?

Future aims to elucidate the biological role of TRPV4 regulation in skin

In future studies, we suggest that investigations be conducted to correlate the expression levels of TRPV4 and other TRP ion channels in keratinocytes with clinical parameters, especially markers of malignancy in non-melanoma skin cancer. This applies also to acute and chronic UVB-induced dermatoses, and to precancerous states that can lead to non-melanoma skin cancer, induced by UVB, UVA, or chemical carcinogens. Furthermore, does TRPV4 downregulation correlate with the development of early dysplasia, late dysplasia, and early malignancy in UVB-induced epidermal skin tumors? With respect to skin cancer and other skin conditions, do TRPV4 expression levels correlate with the impairment in barrier function (Denda et al., 2007), presence of pain, pruritus, and/or inflammation?

Chronically UVB-damaged skin should be studied to determine whether TRPV4 is upregulated (Moore et al., 2013), or rather becomes repressed, after exposure. It will be relevant to determine the point at which this happens.

There is precedence for finding altered TRPV4 regulation in dermatological disease (Sulk et al., 2012), including the RNA-seq database indicating a downregulation of *TRPV4* mRNA in psoriasis (Li et al., 2014): a benign inflammatory hyperproliferative skin disease. These observations reiterate the need to investigate these highly relevant, yet also complex scientific questions of TRPV4 regulation in keratinocytes with appropriate care. Therefore, a multipronged comparison needs to be conducted: UVB-mediated vs. non-UVB-mediated inflammatory skin diseases vs. noninflammatory proliferative disorders vs. precancerous states vs. benign vs. malignant keratinocyte-derived tumors. Cohorts need to be sufficiently large to conclusively determine the role of TRPV4 expression. This approach has to take into account mRNA and protein abundance of TRPV4, and—where feasible—its functional expression as a channel. Additional relevant questions concern the identities of the downstream signaling cascades as well as the gene-regulatory events upstream of *TRPV4* gene expression. With respect to the latter, is TRPV4 downregulation in skin cancer a (direct) result of persistent inflammation, chronic UVB exposure, or epithelial proliferation, or is it caused by malignant transformation?

Conclusion

We anticipate that the findings from Nassini’s and Massi’s groups will precipitate discussion about mechanisms underlying keratinocyte-derived skin cancer growth: TRPV4 as a keratinocyte-derived UVB detector is downregulated in these cells during tumor progression, perhaps in a “protective” autoregulatory, local homeostatic manner. The relevant mechanisms are yet to be discovered. TRPV4 downregulation could lead to uncontrolled tumor growth of keratinocytes; however, it could also exert a more growth-antagonistic role in cells that no longer obey physiological growth and differentiation.

Thus, we are curious whether reestablishing TRPV4 expression in malignant (or pre-malignant) skin keratinocytes could be therapeutic, or whether it would eventually aggravate dysregulated growth and enhance the metastatic capacity of keratinocyte malignancies (see

also the effect of TRPV4 activation in human airway epithelia on activated RAS and enhanced MMP-1 expression (Li et al., 2009; 2011)).

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Clinical Implications

- Epidermal squamous cell and basal cell skin cancer: is TRPV4 channel downregulation in keratinocytes a novel tumor marker?
- Relevance of TRPV4 ion channel function for skin carcinogenesis can now be examined.
- This represents an intriguing observation, because TRPV4 in epidermal keratinocytes is activated by UVB radiation, which causes direct tissue injury and pain.