TRP channels in skin: from physiological implications to clinical significances

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TRP channels are expressed in various cells in skin. As an organ system to border the host and environment, many nonneuronal cells, including epidermal keratinocytes and melanocytes, express several TRP channels functionally distinct from sensory processing. TRPV1 and TRPV3 in keratinocytes of the epidermis and hair apparatus inhibit proliferation, induce terminal differentiation, induce apoptosis, and promote inflammation. Activation of TRPV4, 6, and TRPA1 promotes regeneration of the severed skin barriers. TRPA1 also enhances responses in contact hypersensitivity. TRPCs in keratinocytes regulate epidermal differentiation. In human diseases with perturbed epidermal differentiation, the expression of TRPCs are altered. TRPMs, which contribute to melanin production in melanocytes, serve as significant prognosis markers in patients with metastatic melanoma. In summary, not only act in sensory processing, TRP channels also contribute to epidermal differentiation, proliferation, barrier integration, skin regeneration, and immune responses. In diseases with aberrant TRP channels, TRP channels might be good therapeutic targets.

Key words: TRP channels, keratinocytes, skin

Skin is the largest organ in the human body. It is composed of three major components (Fig. 1). The superficial component is the epidermis, which includes several layers of keratinocytes. Basal keratinocytes in epidermis proliferate to generate suprabasal keratinocytes, which undergo further differentiation, eventually to the cells devoid of nuclei in the corneal layer. These corneal keratinocytes, also termed terminal differentiated cells, together with the dense intercellular structures, make up the delicate and solid skin barriers. The intact skin barrier prevents noxious substance and pathogens enter into human body and prevents water vaporization from inside. Melanocytes reside near basal keratinocytes. Melanocytes produce melamins and transfer the melamins to adjacent keratinocytes. Langerhans cells, the professional antigen presenting cells in the epidermis, capture foreign or endogenous antigens, migrate to regional lymph nodes to prime specific clones of T cells. The middle component of skin is the dermis. The dermis includes extracellular matrix, collagens, as well as endothelial cells, mast cells, and fibroblasts. The dermis provides the nutritional and vascular network and contributes mainly to the physical property of the skin. Abnormal wound healing may occur with excess deposition of extracellular matrix and/or collagens as well as fibroblast and vessels. The dermis also provides a transit for the peripheral nerve endings from the epidermis to the deep skin. The deep component of skin is the subcutaneous tissue, which provides adequate heat insulation and serve as energy storage.

As an integrative system, skin mediates the sensory function, provides an immunological barrier, maintains skin homeostasis, and produces melanin pigments. Based on the available evidences, the TRP channels might play a role in mediating or regulating these physiological functions. Furthermore, the perturbation in the function and/or in the expressions of TRP channels can contribute to skin inflammation, abnormal differentiation, pigmentary diseases, and perhaps carcinogenesis.

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increased in the epidermal keratinocytes \[3\]. Interestingly, certain endogenous molecules that promote TRPV1 activity (including ATP, prostaglandins and histamine) are also potent pruritogens \[2,4\]. In humans, histamine-induced itch is mediated, at least in part, by TRPV1 \[5\]. In line with the data, TRPV1 knockout mice have impaired scratching behavior induced by histamine \[6\]. Intriguingly, depletion of TRPV1 expressing neurons by capsaicin is associated with intense itch, scratching, and ulcers \[7\]. These data suggest that TRPV1 might be involved in the perception of itch, however, more neurological and physiological data is warranted.

Role of TRPV1 in the control of skin growth, skin cell survival and cutaneous inflammation

TRPV1 is expressed in a variety of skin cells, including epidermal keratinocytes, mast cells, Langerhans cells, and sebocytes. TRPV1 mostly shows primarily growth-inhibitory functions in the epidermis. TRPV1 is known to regulate keratinocytes growth and differentiation. In cultured keratinocytes, TRPV1-mediated calcium entry inhibits cell proliferation and enhances apoptosis \[8,9\]. TRPV1 activation by capsaicin regulates the epidermal permeability barrier \textit{in vivo} \[10\].
TRPV1 defected mice have impaired hair cycles due to delayed catagen phase [13]. In vitro, TRPV1 activation in human SZ95 sebocytes inhibits sebum production through alternation of genes of lipid homeostasis [14].

TRPV3 is highly expressed in cutaneous keratinocytes [15]. In mice, TRPV3 enhances regeneration of epidermal barrier formation and promotes morphogenesis of hair apparatus. This may occur through the formation of a signaling complex between TRPV3 and the EGFR [16]. Consistent with this concept, TRPV3 knockout mice demonstrated hair abnormalities, including wavy hair coat and curly whiskers [16,17]. On the other hand, constitutively active TRPV1 defected mice have impaired hair cycles due to delayed catagen phase [13]. In vitro, TRPV1 activation in human SZ95 sebocytes inhibits sebum production through alternation of genes of lipid homeostasis [14].

**Table 1** Expression and function of TRP channels in nonneuronal cells of skin

| Keratinocytes | Outer root sheath cells in hair follicle | Implications |
|---------------|----------------------------------------|--------------|
| **TRPV1**     | Activation: Calcium entry, antiproliferation, proapoptosis [52,53], Delayed barrier recovery [10], Proinflammation (IL-1, -8, PGE2, TGFβ2, MMP-1) [8,54,55], Induced by UV [11] TRPV1 KO is impaired in skin inflammation [56] | Activation: Proapoptosis, proinflammation [8], Impaired hair shaft elongation [8] Proinflammation (IL-1, -8, PGE2, TGFβ2, MMP-1) [8] Induced by UV [12] | Increased expressions in prurigo nodularis [3] and aged skin [57]. PAC-14028 TRPV1 antagonist improves atopic-like skin in mice [58] TRPV1 KO are tumor-prone [59] |
| **TRPV3**     | Antiproliferation and proapoptosis [19], Release of NO [60], cytokines, PGE2 [8], Promotion of cell migration and wound healing [50] TRPV3 KO have impaired skin barrier; wavy hair coat, curly whiskers [16] | Impaired hair shaft elongation [19,61] | TRPV1 “Gain-of-function” mutation results in pruritic AD like skin [18,21] Human Olmsted syndrome by Gly573Ser mutation manifests as mutilating palmoplantar keratoderma [62] |
| **TRPV4**     | Enhancing barrier regeneration [10] TRPV4 KO have impaired skin barrier, poor differentiation [63] |
| **TRPV6**     | Calcium entry, terminal differentiation, and wound repair [64] TRPV6 KO have impaired skin barrier, decreased calcium content [65] |
| **TRPA1**     | Increased barrier regeneration [25] Increased calcium entry [24] Modulate differentiation [66] Proinflammation and enhanced contact hypersensitivity [27] TRPA1 KO have decreased response to urushiol [28] |
| **TRPCs** (TRPC1, 4, 5, 6, 7) | Expressed majorly in differentiated keratinocytes [42,67] TRPC1/4: keratinocyte differentiation [44] TRPC6: antiproliferation and induces differentiation [45] Darier’s disease: TRPC1-mediated calcium entry is impaired [26,46] | Myofibroblast transformation: TRPC6 [68] Impaired calcium entry in keratinocytes from patients with psoriasis [69] TRPC6-induced calcium in keratinocytes from actinic keratosis inhibits cell proliferation and induces differentiation [70] |

In terms of inflammation, TRPV1 activation by capsaicin in human epidermal keratinocytes causes release of several pro-inflammatory cytokines [8]. UV irradiation increases TRPV1 expression in human skin [11]. TRPV1 in keratinocytes mediates the UV-induced production of MMP1 [12], an enzyme that is implicated in skin inflammation and wound repair. These findings in TRPV1 suggest that TRPV1 modulators may be beneficial in the treatment of several diseases, including photodermatosis, acne vulgaris, and hair disorders.

Regarding to hair morphogenesis, capsaicin induces TRPV1 activation, inhibiting hair shaft elongation and inducing catagen regression. In vitro study showed that TRPV1 activation was associated with differential gene expressions and differential production of cytokines and growth factors, many of which control hair growth in human [9]. In mice,
TRPA1

Skin irritants such as mustard oil, nicotine, and cinnamaldehyde, could activate TRPA1 [23]. Analogous to TRPVs, TRPA1 activation by cold or chemicals enhances the regeneration of skin barrier, along with an increase in intracellular calcium [24]. On the other hand, TRPA1 inhibition markedly impairs the recovery of skin barrier [25]. In terms of skin inflammation, TRPA1 activation by cinnamaldehyde application induces skin inflammation through release of Substance P [26]. Contact hypersensitivity reaction is impaired when a TRPA1 antagonist, HC030031, is given [27]. In parallel, TRPA1-defected mice showed an diminished skin inflammation and contact dermatitis caused by oxazolone and urushiol [27,28].

TRPMs

Melanocytes play an important role in the production of melanin, which is important in the intrinsic defense of skin against UV. Furthermore, the most notorious skin cancer with awful prognosis, is the malignant melanoma developed from abnormal clones of melanocytes. TRPM (melastatin TRP) channels control several physiological functions in melanocytes. Human melanocytes express TRPM1, which mediates the production of melanosomes [29,30]. In melanoma cells, TRPM1 channels are pro-apoptotic [31]. In tissues, TRPM1 expressions are decreased in the samples from metastatic melanoma [32,33]. The miRNA211, coded by an intron of TRPM1, may mediate its tumour-promoting effect [34]. Because of its pro-apoptotic effects, many of the researchers and studies suggested that TRPM1 may serve as a good prognostic marker for metastatic melanoma. For TRPM2, overexpression of wild-type TRPM2 in melanoma cell cultures induces apoptosis [35]. For TRPM7, decreased and/or faulty TRPM7 production leads to impaired melanocytic differentiation [36], which can result in vitiligo, a depigmented skin disease with spontaneous loss of epidermal melanocytes.
TRPM8, analogous to TRPA1, can be activated by cold stimuli and several chemicals, such as menthol, eucalyptol, icilin [15,37,38]. TRPM8 gene is also expressed in melanoma cells and tissues. TRPM8 activation in human melanoma cells suppresses cell viability, possible due to calcium-dependent cell death [39,40]. In addition to its role in melanocytes, TRPM8 also regulates the barrier function of epidermal keratinocytes. Topical application of TRPM8 activator WS12 in mice accelerated barrier repair [41], suggesting TRPM8 may be also involved in regulating epidermal homeostasis.

TRPCs

In keratinocytes, not only TRPV1 and TRPV3 are expressed but also other TRP channels. These channels include TRPC1, TRPC4, TRPV4, TRPV5, TRPA1, TRPM8 [42,43]. The detailed functions of these TRP channels remains largely uncertain but they may be involved in the regulation of ordered epidermal differentiation, barrier functions, and abnormal transformation [44,45]. In basal cell carcinoma, the most common skin cancer, TRPC1 and TRPC4 are absent [44]. In Darier’s disease, a disease of abnormal differentiation and keratinization by mutations in the endoplasmic reticulum (ER) Ca2+ ATPase ATP2A2 (protein SERCA2), the TRPC1 is overexpressed [46].

The talk between keratinocytes and nerve endings

Since nerve endings apparently penetrate into the epidermis and the epidermis is majorly composed of keratinocytes, it is likely keratinocytes might sense the physical and chemical stimulations and mediate the signal to the surrounding nerve endings as innervated by dorsal root ganglia or neurons. However, little is known about the signaling molecules between keratinocytes and nerve endings. By using a coculture model, Sondersorg et al. reported that ATP serves as the mediating transmitter molecule released from keratinocytes to the neurons [47]. Knockout experiments showed that the opioid receptor pathway regulates skin homeostasis, epidermal nerve fiber regulation, and pathophysiology of itching as revealed by that opioid receptor knockout mice have significant thinner epidermis and a higher density of free nerve endings than the wild-type counterparts [48]. Keratinocytes irradiated with UV release nitric oxide [49], which was shown to mediate TRPV3-associated thermosensory behaviors in vivo [50]. Finally, the balance between nerve growth factor (NGF), and semaphorin 3A (SemA3A) from keratinocytes was shown to regulate the sensory nerve density in the epidermis [51].

Conclusions

TRPV1 in nerve endings and neurons is involved in the itch perception. TRPV1 and TRPV3 are expressed in keratinocytes of epidermis and hair apparatus. TRPV1 and TRPV3 inhibit proliferation, induce terminal differentiation, induce apoptosis, and promote inflammation. Activation of TRPV4, 6, and TRPA1 promotes regeneration of the severed skin barriers. Besides, TRPA1 activation enhances responses in contact hypersensitivity. TRPCs in keratinocytes involve in epidermal differentiation. In diseases with perturbed differentiation such as actinic keratosis, psoriasis, and Darier’s disease, the expression of TRPCs are altered. TRPs are involved in the pigment production from melanocytes and they might provide significant prognosis markers in patients with metastatic melanoma. Not only act in sensory processing, TRP channels also contribute to epidermal differentiation, proliferation, barrier integration, skin regeneration, and cutaneous immune responses. In diseases with abnormal functions and expressions of TRP channels, TRP channels might be good therapeutic targets.

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Conflict of Interest

All the authors declare no conflict of interests.

Author Contributions

H. J.-C. collected, reviewed the literatures, and drafted the manuscript. L. C.-H. edited the manuscript and approved the final form.

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