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Themed Section: The pharmacology of TRP channels

REVIEW

TRP channels in the skin

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Emerging evidence suggests that transient receptor potential (TRP) ion channels not only act as 'polymodal cellular sensors' on sensory neurons but are also functionally expressed by a multitude of non-neuronal cell types. This is especially true in the skin, one of the largest organs of the body, where they appear to be critically involved in regulating various cutaneous functions both under physiological and pathophysiological conditions. In this review, we focus on introducing the roles of several cutaneous TRP channels in the regulation of the skin barrier, skin cell proliferation and differentiation, and immune functions. Moreover, we also describe the putative involvement of several TRP channels in the development of certain skin diseases and identify future TRP channel-targeted therapeutic opportunities.

LINKED ARTICLES

This article is part of a themed section on the pharmacology of TRP channels. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-10

Abbreviations

5-HT, 5-hydroxytryptamine (serotonin); AD, atopic dermatitis; AHA, α-hydroxyl acid; ATP, adenosine 5'-triphosphate; BCC, basal cell carcinoma; BTCT, N-(4-t-butylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carboxamide; CGRP, calcitonin gene-related peptide; DAR, Darier's disease; HF, hair follicle; IL, interleukin; KO, knockout; NO, nitrogen monoxide; ORS, outer root sheath; OS, Olmstead syndrome; PGE_2, prostaglandine E2; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; SP, substance P; SSC, squamous cell carcinoma; TCA, trichloroacetic acid; TE, tumour-enriched; TGFβ2, transforming growth factor β2; TRP, transient receptor potential; TRPA, transient receptor potential ankyrin; TRPC, transient receptor potential cannonical; TRPM, transient receptor potential melastatin; WS12, (1R*,2S*)-N-(4-methoxyphenyl)-5-methyl-2-(1-methylethyl)cyclohexanecarboxamide

The skin is one of the largest organs of the human body; therefore, it exhibits a plethora of physiological and homeostatic regulatory mechanisms (see reviewed in Bukowskiy, 2009; Draelos and Pugliese, 2011; Oláh *et al.*, 2012). Indeed, the skin (i) establishes and maintains the first line defence of the organism against various forms of physical, chemical, and biological harmful stimuli and challenges (barrier functions); (ii) is a highly active neuro-immuno-endocrine organ (actually, the skin and the nervous system have the same embryological origin; see Makrantonaki *et al.*, 2010) as: the skin-localized sensory afferents are involved in the neuronal processing of multiple sensory modalities (e.g. pain, itch, touch, thermosensation); it functionally expresses all major humoral and cellular components of the innate and adaptive immunity ('skin immune system'); it is not only the target but also the source of several hormonal systems (e.g. vitamin D family, hypothalamic-pituitary-adrenal and hypothalamic-pituitary -thyroid axis hormones; Zouboulis, 2004; 2009b); (iii) also maintains proper motor (e.g. piloerection, vasoregulation), exocrine (e.g. sweat and sebum production) and transport functions. Of further importance, pathological alterations in these mechanisms result in the development of such prevalent dermatoses such as atopic dermatitis (AD), psoriasis, acne vulgaris, various forms of dermatitis, hair growth disorders and cutaneous malignancies.

Emerging evidence suggests that multiple transient receptor potential (TRP) channels (see Alexander *et al.*, 2013a) are critically involved in the regulation of the above cutaneous functions. TRP channels, which were originally described as 'polymodal cellular sensors' (Clapham, 2003; Damann *et al.*, 2008; Vay *et al.*, 2012) that can be activated by various physical, chemical and thermal stimuli (Ramsey *et al.*, 2006; Vriens *et al.*, 2008; 2009), are now considered as 'promiscuous pleiotropic molecules' as the above 'afferent' functions can be supplemented by 'effector' roles. Indeed, TRP channels are involved in cellular homeostasis and growth control, regulation of cell fate and survival, immune and inflammatory mechanisms, and endocrine and exocrine secretory processes (Nilius and Owsianik, 2010; Boesmans *et al.*, 2011; Denda and Tsutsumi, 2011; Moran *et al.*, 2011; Fernandes *et al.*, 2012).

Recent excellent reviews elegantly summarize the plethora of evidence on the 'afferent' roles of multiple TRP channels in mediating the peripheral and central processing of pain, itch and thermal sensation (Nilius *et al.*, 2012; 2013; Akiyama and Carstens, 2013; Brederson *et al.*, 2013; Lucaciu and Connell, 2013; Tóth and Bíró, 2013). Therefore, in the current review, we have focused on the 'efferent' roles of various TRP channels, expressed by various non-neuronal cell populations of the skin, in the regulation of skin homeostasis under physiological conditions. Specifically, we present data indicating the involvement of TRP channels in the (i) formation and maintenance of physico-chemical skin barrier; (ii) skin cell and organ growth and differentiation; and (iii) cutaneous immunological and inflammatory processes. Moreover, we also describe the (potential) participation of certain TRP channels in the development of specific skin diseases and identify putative TRP channel-targeted therapeutic opportunities for the clinical management of these (often very highly prevalent) conditions.

TRPV1

In the skin, the 'capsaicin receptor' (Caterina *et al.*, 1997; 2000) was first identified on a subset of nociceptive sensory nerve endings and was shown to be involved in 'classical' sensory afferent functions (sensation of pain, itch, warm, chemical stimuli) as well as in local (neurogenic inflammation via the local release of several neuropeptides) and systemic (release of analgesic neuropeptides) efferent functions (reviewed in Szallasi and Blumberg, 1999; Caterina and Julius, 2001; Clapham, 2003; Szolcsányi, 2004; Dhaka *et al.*, 2006; Vriens *et al.*, 2008; 2009; Eid and Cortright, 2009; Bodkin and Fernandes, 2013). Importantly, although a few contradictory findings have also been published (Pecze *et al.*, 2008; Cavanaugh *et al.*, 2011), numerous studies have identified TRPV1 on several non-neuronal populations of skin cells (such as keratinocytes, mast cells, Langerhans cells and sebocytes) (Denda *et al.*, 2001; Inoue *et al.*, 2002; Southall *et al.*, 2003; Bodó *et al.*, 2004; 2005; Ständer *et al.*, 2004; Bíró *et al.*, 2006; Tóth *et al.*, 2009a,b; 2011), which suggest that it has a functional role in cutaneous 'non-sensory' functions.

Role in skin cell growth control and barrier functions

Epidermal keratinocytes are key components of the physical/chemical skin barrier. To execute this role, keratinocytes perform a continuous, apoptosis-driven differentiation programme that strongly depends on a gradual increase in intracellular [Ca^{2+}] towards the upper layers of the epidermis (reviewed in Proksch *et al.*, 2008; Jensen and Proksch, 2009; Rawlings, 2010). Therefore, agents that modulate intracellular [Ca^{2+}] most probably also affect keratinocyte growth and differentiation and hence the epidermal barrier.

Activation of TRPV1 on epidermal keratinocytes and the resulting influx of Ca^{2+} into the cells (Inoue *et al.*, 2002; Southall *et al.*, 2003; Bodó *et al.*, 2004; 2005; Radtke *et al.*, 2011) suppresses cell growth and induces apoptosis (Tóth *et al.*, 2011). Furthermore, after disruption of the epidermal skin barrier in mice, TRPV1 stimulation delayed barrier recovery (Denda *et al.*, 2007) whereas administration of the TRPV1 antagonist PAC-14028 accelerated barrier repair (Yun *et al.*, 2011). In addition, activation of TRPV1 by capsaicin on human sebaceous gland cells suppressed lipid synthesis (Tóth *et al.*, 2009a). As sebaceous lipids also contribute to the establishment of the 'water-proof' skin barrier (see reviewed in Proksch *et al.*, 2008; Jensen and Proksch, 2009; Rawlings, 2010), TRPV1-coupled signalling seems to inhibit the functions of the epidermal physico-chemical barrier.

Of further importance, stimulation of TRPV1 expressed by outer root sheath (ORS) keratinocytes of human hair follicles (HFs) also inhibited hair shaft elongation (assessed in HF organ culture) and proliferation of cultured ORS keratinocytes as well as inducing apoptosis-mediated cell death (Bodó *et al.*, 2005); these phenomena were further confirmed by the results obtained in experiments performed in TRPV1 knockout (KO) mice (Bíró *et al.*, 2006). As various cell populations of the HF are key participants in tissue regeneration, and remodelling in the skin as well as cutaneous wound healing (reviewed in Tiede *et al.*, 2007; Reinke and Sorg, 2012), these data further support the negative role of TRPV1 in the formation and maintenance of the skin barrier.

Role in cutaneous immunological functions

TRPV1 channels expressed by nerve endings of cutaneous sensory afferent fibres play a significant role in the initiation and development of neurogenic inflammation in the skin. Activation of TRPV1 by either capsaicin or by other stimuli results in the local, intracutaneous release of a plethora of neuropeptides, such as substance P (SP) and other tachykinins, as well as calcitonin gene-related peptide (CGRP). The released peptides activate multiple types of skin cells (including keratinocytes, mast cells, professional antigen-presenting cells, fibroblasts, cell populations of the cutaneous blood vessels and sebocytes), located in the immediate vicinity of the sensory endings, and induce the release of certain pro-inflammatory and vasoactive substances. The resulting 'mediator soup', in turn, initiates a complex series of processes (e.g. vasodilatation, oedema formation, invasion of inflammatory cells) collectively referred to as cutaneous neurogenic inflammation (reviewed in Ansel *et al.*, 1997; Luger, 2002; Paus *et al.*, 2006a,b; Peters *et al.*, 2007; Fuchs and Horsley, 2008; Zouboulis, 2009a). For example, it is noteworthy that numerous SP+ immunoreactive nerve fibres were detected in close proximity to the sebaceous glands and expression of the SP-inactivating enzyme neutral endopeptidase was observed within sebaceous germinative cells of acne patients (Toyoda *et al.*, 2002). Moreover, a significant increase in the size of the

sebaceous glands and in the number of sebum droplets in sebocytes was detected on treatment with SP (Toyoda and Morohashi, 2001). As SP was shown to stimulate IL expression in human sebocytes *in vitro* (Lee *et al.*, 2008a), these data collectively support the existence of the above network.

Apparently, TRPV1 expressed by the majority of the above non-neuronal cell types is also involved in the development of (non-neurogenic) skin inflammation. Indeed, activation of TRPV1 on epidermal or HF-derived ORS keratinocytes leads to the increased synthesis and release of a wide array of pro-inflammatory agents (e.g. IL-1β, IL-8, PGE_2, TGFβ2, MMP-1) (Southall *et al.*, 2003; Bodó *et al.*, 2005; Li *et al.*, 2007; Lee *et al.*, 2008b; Jain *et al.*, 2011). Furthermore, TRPV1 and related signalling were also suggested to participate in the pro-inflammatory response induced by UV irradiation of cultured epidermal keratinocytes *in vitro* (Lee *et al.*, 2009b) and in mice *in vivo* (Lee *et al.*, 2011). The pro-inflammatory role of TRPV1 is also supported by the observation that the release of certain cytokines evoked by application of TCA is impaired in TRPV1-deficient mice (Li *et al.*, 2012).

Interestingly, cutaneous TRPV1 signalling might also exert contradicting, that is, anti-inflammatory effects. Indeed, in human sebocytes in culture, stimulation of TRPV1 by capsaicin suppressed the level of pro-inflammatory IL-1β (Tóth *et al.*, 2009a). Likewise, activation of TRPV1 inhibited the differentiation, maturation and pro-inflammatory cytokine release of human monocyte-derived dendritic cells (Tóth *et al.*, 2009b).

Role in skin pathophysiology and cutaneous diseases

Although we still lack an exact mechanistic proof on its role, TRPV1 (similar to other TRP channels, see below) seems to be involved in the development of a wide array of skin diseases. Indeed, elevated TRPV1 expression was identified in the pathological skin lesions of prurigo nodularis patients (Ständer *et al.*, 2004) as well as in UV-irradiated photo-aged and intrinsically aged skin (Lee *et al.*, 2009a; 2012). Interestingly, conflicting with the above findings, locally applied acute UVC irradiation significantly down-regulated the mRNA expression of TRPV1 in human skin (Weinkauf *et al.*, 2012). From the functional-pharmacological aspect, it is noteworthy that treatment of prurigo patients with topical capsaicin, most probably due to its aforementioned anti-proliferative and pro-apoptotic cellular effects on epidermal keratinocytes (see above), resulted in a marked improvement in hyperkeratotic skin lesions (Ständer *et al.*, 2001). In addition, other skin conditions have also been shown to respond to capsaicin including, for example, cutaneous erythema (erythema e pudori) (Nielsen *et al.*, 2013), skin inflammation (Desai *et al.*, 2013), sensitive skin (Kueper *et al.*, 2010), apocrine chromhidrosis (Gandhi *et al.*, 2006) and notalgia paresthetica (Wallengren, 1991). Of further importance, oral administration of the TRPV1 antagonist PAC-14028 in an experimentally-induced model of atopic dermatitis (AD) in mice strikingly improved the AD-like systemic and local symptoms (Yun *et al.*, 2011). Recently, it has been reported that the TRPV1 response to capsaicin stimulation is decreased and scratching behaviour evoked by non-histaminergic itch inducers impaired in NC/Tnd mice with spontaneously developed AD-like skin lesions (Amagai *et al.*, 2013). Furthermore, genetic deletion of TRPV1 in mice leads to an increased susceptibility of the animals to skin tumour formation (Bode *et al.*, 2009), which indicates that TRPV1 have a protective role against cutaneous malignant transformation and carcinogenesis. Finally, it should be mentioned that, in affected skin of patients with various types of rosacea, altered expression patterns for TRPV1, TRPV2, TRPV3 and TRPV4 were identified; this suggests the possible involvement of multiple TRPVs in the pathogenesis of rosacea (Sulk *et al.*, 2012). Taken together, these data imply that TRPV1 might be a novel therapeutic target in certain skin diseases.

Role in mediating the dermatological side effects of certain pharmacotherapies

Interestingly, the antifungal agent clotrimazole has been found to activate TRPV1 (as well as TRPA1 but to inhibit TRPM8), and these mechanisms might contribute to the burning, itching sensation associated with some cases of topical applications of clotrimazole (Meseguer *et al.*, 2008). It was also shown that retinoids widely used to treat numerous skin diseases may activate TRPV1 and can evoke nocifensive behaviour, CGRP release from sensory endings and inflammatory hyperalgesia (Yin *et al.*, 2013). Therefore, the multimodal activation mechanisms of TRPV1 suggest that the channel is not only a potential therapeutic target of various dermatoses but may also act as a potential 'mediator' of some dermatological side effects associated with systemic or topical application of certain medications.

TRPV3 and TRPV4

Among the large number of TRP channels expressed in the skin, TRPV3 (and TRPV4) possibly plays the most prominent role in the regulation of skin functions (Nilius and Bíró, 2013; Nilius *et al.*, 2013). Actually, TRPV3 was originally demonstrated to be most abundantly expressed on epidermal keratinocytes both in humans and rodents (Smith *et al.*, 2002; Xu *et al.*, 2002; Peier *et al.*, 2002b; Grubisha *et al.*, 2014), whereas TRPV4 was found in several tissues (Wissenbach *et al.*, 2000; Liedtke *et al.*, 2000; Strotmann *et al.*, 2000; Delany *et al.*, 2001) including keratinocytes (Suzuki *et al.*, 2003). No wonder, therefore, that both channels were thought to markedly regulate numerous cutaneous biological processes.

Role in skin cell growth control and barrier functions

Importantly, TRPV3 KO mice exhibit a pathologically altered epidermal barrier (Cheng *et al.*, 2010). This is most probably due to the fact that, in the surface membrane of epidermal keratinocytes, TRPV3 is co-expressed in a functional signaloplex with the EGF receptor (ErbB1; see Alexander *et al.*, 2013b) as well as with TGFα, key members of the signalling pathways that regulate the homeostatic establishment of the epidermal barrier (see reviewed in Proksch *et al.*, 2008; Jensen and Proksch, 2009; Rawlings, 2010). Interestingly, mice lacking the *trpv3* gene also exhibit hair phenotypes (wavy hair coat, curly whiskers), similar to those changes described in mice with mutations in the genes for TGFα and the ErbB1 receptor (Murillas *et al.*, 1995), which suggest that TRPV3-coupled signalling also controls growth and survival of the HF. Indeed,

TRPV3 stimulation (similar to the effect of TRPV1, see above) inhibited hair shaft elongation in human HF organ culture and induced apoptosis (catagen regression) (Borbíró *et al.*, 2011). In line with these data, pharmacological or thermal activation of TRPV3 on cultured human ORS and epidermal keratinocytes suppressed cellular growth and evoked cell death (Borbíró *et al.*, 2011; Radtke *et al.*, 2011). These data collectively suggest a role for TRPV3 in controlling functions of key keratinocyte 'players' involved in barrier formation.

Furthermore, TRPV3 activation also resulted in the release of NO from keratinocytes, a mediator that plays a significant role in a multitude of cutaneous homeostatic mechanisms including wound healing (Cals-Grierson and Ormerod, 2004). Indeed, TRPV3-dependent release of NO from keratinocytes accelerated keratinocyte migration *in vitro* and stimulated wound healing *in vivo* (Miyamoto *et al.*, 2011) and these effects were dependent on intracellular acidification. Intriguingly, lowering intracellular pH may also play a role in mediating the beneficial effect of certain naturally occurring proton donor α-hydroxyl acids (AHAs), which function as efficient exfoliating agents (hence induce concomitant epidermal turnover) when applied topically in various cosmeceuticals. Importantly, one AHA, glycolic acid, was shown to activate TRPV3 on human epidermal keratinocytes and this resulted in low pH-dependent suppression of cellular viability (Cao *et al.*, 2012).

Similar to TRPV3, TRPV4 is also involved in epidermal barrier homeostasis. Indeed, thermal or pharmacological activation of TRPV4 accelerated barrier regeneration in mice (Denda *et al.*, 2007). In perfect agreement with these data, characteristics of an impaired epidermal barrier (leaky cell-cell junctions, non-physiological actin rearrangement, insufficient stratification) were observed in TRPV4-deficient mice (Sokabe *et al.*, 2010; Sokabe and Tominaga, 2010). The importance of TRPV4 and junctional proteins is further supported by studies performed on cell cultures. Indeed, in cultured human epidermal keratinocytes and human skin organ cultures, TRPV4 is functionally co-expressed with certain junctional proteins (e.g. β-catenin and E-cadherin), which are also essential for the proper epidermal barrier (Kida *et al.*, 2012). Furthermore, pharmacological activation of TRPV4 strengthens the tight-junction barrier between human epidermal keratinocytes, as shown by an augmented junctional protein (claudin-4, occludin) expression, increased transepithelial electric resistance, and decreased paracellular diffusion of labelled molecules through keratinocyte sheets (Akazawa *et al.*, 2013).

'Gain-of-function' mutations in the trpv3 *gene*

Besides the above experimental data, the discovery of certain mutations of the *trpv3* gene in mice and in humans has provided 'real' mechanistic evidence for the pivotal role of TRPV3-coupled signalling in the physiological and pathological regulatory processes of the skin. Indeed, the 'gain-of-function' mutation (mostly $Gly^{573}Ser$) of the *trpv3* gene, resulting in permanently opened TRPV3 ion channels (Xiao *et al.*, 2008), was shown to be responsible for the spontaneously hairless phenotype found in DS-*Nh* mice and in WBN/Kob-Ht rats (Asakawa *et al.*, 2006; Imura *et al.*, 2007; Yoshioka *et al.*, 2009). In addition, by presenting the aberrant expressions of certain 'hair genes' (encoding keratin-associated proteins) in the skin of these animals, it was also suggested that TRPV3 is essential for proper hair development (Imura *et al.*, 2007) (a phenomenon that was repeated in human HF organ culture, see above).

Intriguingly, this 'gain-of-function' mutation of the *trpv3* gene as well as transgenic, cell-specific overexpression of the mutant $TRPV3Gly^{573}Ser$ channels in epidermal keratinocytes in mice resulted in the development of a pruritic and hyperkeratotic skin inflammation, whose local and systemic signs – such as intracutaneous and systemic elevation of a multitude of pro-inflammatory cytokines, increased levels of nerve growth factor that plays a role in the pathogenesis of AD in humans, engagement of mast cells and certain lymphocyte populations – greatly resemble those of human AD (Asakawa *et al.*, 2006; Xiao *et al.*, 2008; Yoshioka *et al.*, 2009). Likewise, the above 'gain-of-function' mutation was also found to be involved in the development of hapten-induced dermatitis in mice (Imura *et al.*, 2009). These data collectively suggest that TRPV3 activation promotes skin inflammation.

Experiments performed on cultured human keratinocytes further support the pro-inflammatory role of TRPV3. Pharmacological stimulation of this channel by certain plant-derived substances (e.g. eugenol, carvacrol, thymol) induced various degrees of skin irritation and, as heat also did, evoked release of pro-inflammatory ILs and PGE2 (Xu *et al.*, 2006; Huang *et al.*, 2008). Because many pro-inflammatory mediators (PGE_2 itself as well as bradykinin, histamine and ATP) were shown to sensitize TRPV3 (Mandadi *et al.*, 2006; Huang *et al.*, 2008; Phelps *et al.*, 2010), TRPV3 activation might initiate a positive feedback loop, which further accelerates the development of skin inflammation. Furthermore, the endogenously produced ω-3 lipid metabolism product, 17(R)-resolvin D1, which was shown to exert potent anti-inflammatory and pro-resolving actions, was found to specifically block the activity of TRPV3 channels expressed by cultured epidermal keratinocytes (Bang *et al.*, 2012).

Further information about the role of TRPV3 in skin biology was obtained from investigating patients suffering from Olmsted syndrome (OS) (also known as 'Mutilating palmoplantar keratoderma with periorificial keratotic plaques' or 'Polykeratosis of Touraine'). OS is a rare congenital dermatosis, which is characterized by multiple skin symptoms such as palmoplantar and perioral keratosis and keratoderma, diffuse hair loss and extremely intense pruritus (Lin *et al.*, 2012). Actually, these skin alterations are strikingly similar to those described in mice and rats with the aforementioned $Gly^{573}Ser$ mutation of the *trpv3* gene (see above). Of greatest importance, the same (as well as other $Gly^{573}Cys$ and $Trp^{692}Gly$) 'gain-of-function' *trpv3* mutations were identified in keratinocytes of the OS patients (Lai-Cheong *et al.*, 2012; Lin *et al.*, 2012), and the constitutively opened TRPV3 channels, most probably via a profuse Ca^{2+} influx and the concomitant keratinocyte death, result in the above symptoms. Finally, it should also be mentioned that a recent case study of an OS patient identified a novel $Gly^{573}Ala$ point mutation of the *trpv3* gene; in this individual, a profound cutaneous and systemic immune dysregulation with dermal infections, hyper-IgE synthesis and persistent eosinophilia was identified (Danso-Abeam *et al.*, 2013). Therefore, OS can be regarded as the first identified cutaneous 'TRPathy'.

TRPV6

Similar to other TRPV members, the highly Ca^{2+}-permeable TRPV6 is also involved in skin barrier formation and function. Indeed, TRPV6 KO mice exhibit impaired stratum corneum formation, decreased total epidermal Ca^{2+} content and pathological cutaneous Ca^{2+} gradient (Bianco *et al.*, 2007). In line with these *in vivo* data, in cultured keratinocytes, TRPV6 was shown to be crucially involved in the terminal differentiation process (exemplified by the orchestrated expression of cytokeratins, involucrin and transglutaminase 1; formation of intercellular junctions; stratum corneum keratinization) induced by the elevation of extracellular [Ca^{2+}] (Lehen'kyi *et al.*, 2007). It was also shown that TRPV6-coupled signalling, resulting in the elevation of the intracellular [Ca^{2+}], plays a key role in the development of the cellular effects of vitamin D3 to promote keratinocyte differentiation (Bouillon *et al.*, 2006; Lehen'kyi *et al.*, 2007). Likewise, TRPV6-mediated Ca^{2+} entry in human cultured epidermal keratinocytes was found to be involved in mediating the putative pro-differentiating (augmented levels of involucrin and cytokeratins 1 and 10) and skin repairing effects of Avène Thermal Spring water; interestingly, the this water also elevated the expression of TRPV6 channels in keratinocytes (Lehen'kyi *et al.*, 2011).

TRPA1

Similar to TRPV1, the cold-sensitive TRPA1 of the ankyrin family, which can also be activated by skin irritants such as mustard oil, formalin, nicotine, allyl isothiocyanate and cinnamaldehyde (Bandell *et al.*, 2004; Jordt *et al.*, 2004; McNamara *et al.*, 2007; Karashima *et al.*, 2009; Talavera *et al.*, 2009), was demonstrated on TRPV1-expressing nociceptive sensory neurons (Story *et al.*, 2003; Kobayashi *et al.*, 2005). Therefore, again similar to TRPV1, TRPA1 is also involved in the afferent processing of various sensory modalities (cold, pain, itch), as well as in mediating neurogenic inflammation (Dhaka *et al.*, 2006; Nilius and Mahieu, 2006; Ramsey *et al.*, 2006; Nilius *et al.*, 2007).

Role in skin cell growth control and barrier functions

Apparently, similar to certain TRPVs, TRPA1 is also involved in regulating epidermal keratinocyte biology. Administration of the above TRPA1 activators to the skin of mice, in which the epidermal barrier was mechanically disrupted, increased the rate of barrier regeneration. Likewise, application of cold stimuli to the skin resulted in similar barrier-promoting effect, which was realized by an augmented secretion of lamellar bodies (part of the epidermal barrier) (Denda *et al.*, 2010b). Importantly, the specific TRPA1 antagonist HC030031 not only prevented the above beneficial effects but, when the skin was treated with the antagonist alone, it also markedly delayed barrier healing; these findings suggest that TRPA1 might play a 'constitutively active' role in epidermal barrier homeostasis. In addition, cold or agonist-induced activation of TRPA1, expressed by human cultured epidermal keratinocytes, resulted in a specific (i.e. prevented by HC030031) increase in intracellular [Ca^{2+}] (Tsutsumi *et al.*, 2010). Furthermore, icilin (which equally activates TRPA1 and another cold-sensitive TRP channel, TRPM8, see also below) induced marked changes in the expressions of certain adhesion and extracellular matrix proteins in cultured keratinocytes as well as of molecules regulating cell fate and differentiation (Atoyan *et al.*, 2009; commented in: Bíró and Kovács, 2009). Collectively, these data suggest that TRPA1 on keratinocytes promotes the formation and maintenance of the epidermal skin barrier. Notably, a number of plant-derived TRPA1 ligands, such as cinnamaldehyde and allyl isothiocyanate, may have pharmacological effects that are independent of TRPA1 activation (Everaerts *et al.*, 2011; Mori *et al.*, 2011; Capasso *et al.*, 2012; Alpizar *et al.*, 2013; Gees *et al.*, 2013). This indicates the importance of using TRPA1 gene-deficient mice to demonstrate response specificity.

Role in cutaneous immunological functions

As mentioned above, TRPA1 is involved in the onset of neurogenic inflammation in the skin; however, recent data also suggest that the channel may also take part in non-neurogenic cutaneous inflammatory events. Indeed, the topically applied TRPA1 activator cinnamaldehyde induced skin inflammation characterized by oedema formation and leukocyte infiltration to the affected skin region. However, these two components were differentially affected by aprepitant, an inhibitor of NK_1 tachykinin receptors (see Alexander *et al.*, 2013c), which are activated by SP release from the sensory afferents upon stimulation of neuronal TRPA1. That is, the NK_1 receptor antagonist effectively prevented skin swelling whereas the TRPA1 inhibitor markedly suppressed immune cell migration (Silva *et al.*, 2011).

The role of TRPA1 in cutaneous inflammation was further verified in certain rodent dermatitis models. In a mouse contact hypersensitivity model, TRPA1 activation enhanced the ear swelling response and migration of dendritic cells to draining lymph nodes, and this effect was antagonized by the TRPA1 antagonist HC030031 (Shiba *et al.*, 2012). Furthermore, in an oxazolone-induced contact dermatitis model, it was shown that genetic deletion or pharmacological blockade of TRPA1 resulted in decreased skin oedema, keratinocyte hyperplasia, leukocyte infiltration and the closely related scratching behaviour in mice. Moreover, in the oxazolone challenged skin of TRPA1-deficient mice, a significant decrease was found in the expression of inflammatory cytokines, nerve growth factor, 5-HT and SP. Intriguingly, oxazolone was also shown to activate recombinant TRPA1, further supporting the causal role of the channel in contact dermatitis. Urushiol, the contact allergen of poison ivy, evoked similar responses, which were also diminished in TRPA1 KO mice (Liu *et al.*, 2013). Finally, it should be mentioned that, in accord with the above *in vivo* data, stimulation of TRPA1 on cultured human keratinocytes evoked the production of the pro-inflammatory molecules IL-1α and IL-1β (Atoyan *et al.*, 2009). It can be concluded, therefore, that, again similar to the cutaneous roles of certain TRPVs, TRPA1 apparently also exerts a pro-inflammatory role in the skin, most probably via an orchestrated interplay between neurogenic and non-neurogenic mechanisms.

TRPMs

Multiple members of the melastatin TRP (TRPM) channel family control certain skin functions, especially those related to melanocyte biology. Of further importance, some of them are also suggested to be involved in the development of one of the most aggressive human tumours, malignant melanoma.

Human epidermal melanocytes were shown to express TRPM1. In addition, expression of functional TRPM1 on melanocytes was shown to be essential for the physiological process of pigmentation (Devi *et al.*, 2009; Oancea *et al.*, 2009). As further support for its pro-melanotic role, a decreased expression of the *trpm1* gene has been shown to be associated with the inhomogeneous coat spotting patterns of Appaloosa horses (Bellone *et al.*, 2008). From the pathophysiological point of view, it is noteworthy that expression of the *trpm1* gene was recognized to be down-regulated in the most aggressive metastatic malignant melanoma samples (Deeds *et al.*, 2000; Duncan *et al.*, 2001; Miller *et al.*, 2004; Zhiqi *et al.*, 2004; Lu *et al.*, 2010). Because (i) TRPM1 channels were found to be pro-apoptotic in melanoma cells, and (ii) miRNA211, coded in an intron of *trpm1*, was shown to be responsible for the tumour-promoting effect of TRPM1 (Levy *et al.*, 2010; Mazar *et al.*, 2010; Boyle *et al.*, 2011; Guo *et al.*, 2012), these findings suggest that TRPM1 may serve as a prognostic marker for metastatic malignant melanoma (Deeds *et al.*, 2000; Duncan *et al.*, 2001; Miller *et al.*, 2004; Zhiqi *et al.*, 2004).

TRPM8 – which, similar to TRPA1, can be activated by cold stimuli and various 'cooling' agents such as menthol, eucalyptol, icilin (McKemy *et al.*, 2002; Peier *et al.*, 2002a; Bautista *et al.*, 2007; Colburn *et al.*, 2007) – was also identified in melanoma cells and samples. Similar to TRPM1, activation of TRPM8 on human cultured melanoma cells suppressed cell viability, most probably via a TRPM8-mediated elevation of intracellular [Ca^{2+}]-dependent cell death (Slominski, 2008; Yamamura *et al.*, 2008). However, in contrast to findings obtained with the *trpm1* gene, markedly decreased levels of TRPM8-specific transcripts were identified in malignant melanoma samples (Tsavaler *et al.*, 2001). The clinical and pathophysiological significance of this latter finding is still to be determined.

Apparently, TRPM8 is also involved in regulating the biology of epidermal keratinocytes; menthol or the TRPM8 activator WS12, when applied topically to the back skin of mice with a mechanically injured skin barrier, highly accelerated barrier repair and this effect was blocked by the TRPM8 antagonist N-(4-t-butylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carboxamide (BTCT) (Denda *et al.*, 2010a). Although the exact significance of TRPM8 expressed by epidermal keratinocytes is still not known (Denda *et al.*, 2010a), these *in vivo* findings suggest that TRPM8 may be involved in regulating epidermal homeostasis.

Finally, two other TRPM channels should be mentioned in relation to malignant melanoma. In melanoma samples, a marked up-regulation of antisense, tumour-enriched (TE) transcripts of TRPM2 was documented (Orfanelli *et al.*, 2008). In line with these results, KO of TRPM2-TE or overexpression of wild-type TRPM2 channels in melanoma cell cultures resulted in a highly increased apoptotic tendency of the cells (Orfanelli *et al.*, 2008). It is also noteworthy that TRPM7 was also identified in human melanoma cell lines; yet, its functional significance is still to be explored.

TRPCs

Several members of the canonical TRPC subfamily were identified in the skin where they mostly control the growth and differentiation of epidermal keratinocytes under physiological and pathological conditions.

Role in skin cell growth control and barrier functions

TRPC1, TRPC4, TRPC5, TRPC6 and TRPC7 were identified in epidermal keratinocytes, especially on the more differentiated cells (Bezzerides *et al.*, 2004; Cai *et al.*, 2005; 2006; Fatherazi *et al.*, 2007). Importantly, in functional studies, TRPC1, TRPC4 and TRPC6 were found to induce the terminal differentiation programme of epidermal keratinocytes. In cultured cells, silencing of TRPC1 or TRPC4 prevented the effect of extracellular [Ca^{2+}] to promote differentiation (Beck *et al.*, 2008), whereas stimulation of TRPC6 suppressed keratinocyte growth and induced differentiation (Müller *et al.*, 2008). Likewise, TRPC6 was also found to be involved in the pro-differentiating actions of triterpenes (shown to halt unwanted growth of tumour cells; Shanmugam *et al.*, 2012), which induced a TRPC6-mediated Ca^{2+} influx and elevated the levels of certain differentiation markers; interestingly, triterpenes also up-regulated TRPC6 expression in epidermal keratinocytes (Woelfle *et al.*, 2010).

Although we lack targeted *in vivo* studies, the above findings collectively suggest an important role for TRPC6 in the formation, maintenance and repair of the cutaneous barrier. Supporting this hypothesis, it was recently shown that TRPC6 is essential and sufficient for myofibroblast transformation, a process by which fibroblasts transdifferentiate to contractile myofibroblasts; these events are key elements of wound healing and tissue remodelling. In line with these data, TRPC6 KO mice showed impaired *in vivo* dermal wound healing after injuries (Davis *et al.*, 2012).

Role in skin pathophysiology and cutaneous diseases

Accumulating evidence suggests that TRPC channels are not only involved in the physiological, homeostatic regulation of skin processes, but also in the pathological events seen in certain dermatoses. Importantly, markedly suppressed levels of all TRPCs (i.e. TRPC1, TRPC4, TRPC5, TRPC6 and TRPC7) were detected in the epidermis *in situ* and on *in vitro* cultured keratinocytes of patients suffering from psoriasis. In addition, exposure of cultured psoriatic keratinocytes to high extracellular [Ca^{2+}] (which, as mentioned above, in normal keratinocytes, leads to the concomitant elevation of intracellular [Ca^{2+}] and the onset of the terminal differentiation programme of the cells) resulted in only minor influx of Ca^{2+}, which is most probably due to the impaired functional expression of the TRPCs in the surface membrane of keratinocytes (Leuner *et al.*, 2011).

The lack of a proper differentiation programme is one of the main pathognomic factors in the development of

Table 1

Roles of TRP channels in various skin diseases

Disease	Potential involvement of TRP channels	Putative therapeutic approaches and supporting evidence
'Barrier-diseases'	*TRPV1* Activation decreased proliferation and induced apoptosis of keratinocytes (Bodó *et al.*, 2005; Tóth *et al.*, 2011). Activation inhibited skin barrier recovery (Denda *et al.*, 2007). Activation induced release of pro-inflammatory cytokines from keratinocytes (Southall *et al.*, 2003; Bodó *et al.*, 2005).	*TRPV1* Antagonism or desensitization might be beneficial. Orally applied TRPV1 antagonist (PAC-14028) accelerated barrier recovery (Yun *et al.*, 2011).
	TRPV4 Activation induced barrier recovery and promoted the tight-junction barrier between keratinocytes (Denda *et al.*, 2007; Kida *et al.*, 2012; Akazawa *et al.*, 2013). Genetic deletion associated with leaky cell-cell junctions (Sokabe *et al.*, 2010; Sokabe and Tominaga, 2010).	*TRPV4* Activation might be beneficial.
	TRPV6 Indispensible for normal epidermal barrier formation and Ca^{2+} homeostasis of keratinocytes (Bouillon *et al.*, 2006; Bianco *et al.*, 2007; Lehen'kyi *et al.*, 2007).	*TRPV6* Activation might be beneficial. Avène Thermal Spring water increased TRPV6 channel expression and initiated a TRPV6-mediated Ca^{2+} entry which, in turn, resulted in differentiation (Lehen'kyi *et al.*, 2011).
	TRPA1 Activation and inhibition accelerated and delayed barrier recovery respectively (Denda *et al.*, 2010b).	*TRPA1* Activation might be beneficial.
	TRPM8 Activation (WS12) potentiated the barrier recovery (Denda *et al.*, 2010a).	*TRPM8* Activation might be beneficial.
	TRPC1/4/6 Promoted differentiation of keratinocytes (Cai *et al.*, 2006; Beck *et al.*, 2008; Müller *et al.*, 2008).	*TRPC1/4/6* Activation might be beneficial.
Skin inflammation (e.g. atopic and contact dermatitis)	*TRPV1* Activation induced release of pro-inflammatory cytokines from keratinocytes (Southall *et al.*, 2003; Bodó *et al.*, 2005).	*TRPV1* Antagonism might be beneficial.
	TRPV3 Gain-of-function mutation resulted in AD-like phenotype in mice (Asakawa *et al.*, 2006; Xiao *et al.*, 2008; Yoshioka *et al.*, 2009).	Antagonism or desensitization might be beneficial.
	TRPA1 It was found to be involved in mediating inflammation induced by various contact irritants/allergens (Liu *et al.*, 2013).	*TRPA1* Antagonism might be beneficial.
Hair growth disorders	*TRPV1* Activation inhibited hair growth (Bodó *et al.*, 2005).	*TRPV1* Antagonism or desensitization might be beneficial in alopecia. Activation might be beneficial in hirsutism.
	TRPV3 Activation inhibited hair growth *in vitro* (Borbíró *et al.*, 2011). Gain-of-function mutation resulted in hairless phenotype in mice (Asakawa *et al.*, 2006; Imura *et al.*, 2007).	*TRPV3* Antagonism or desensitization might be beneficial in alopecia. Activation might be beneficial in hirsutism.
Prurigo nodularis	*TRPV1* Elevated expression was detected in hyperkeratotic lesions of prurigo nodularis patients (Ständer *et al.*, 2004).	*TRPV1* Activation might be beneficial. Chronic topical capsaicin treatment ameliorated the symptoms (Ständer *et al.*, 2001).
Psoriasis	*TRPC1/4/5/6/7* Decreased expression was found (Leuner *et al.*, 2011).	Activation or up-regulation might be beneficial.
Rosacea	*TRPV1-4* Dysregulation of expression was observed (Sulk *et al.*, 2012).	

Table 1

Continued

Disease	Potential involvement of TRP channels	Putative therapeutic approaches and supporting evidence
Acne vulgaris	*TRPV1* Activation inhibited lipid production and suppressed IL-1β synthesis of sebocytes (Tóth *et al.*, 2009a).	*TRPV1* Activation might be beneficial.
Non-melanoma skin cancers	*TRPC1/4* Lack of epidermal expression correlating with tumour cells' proliferation in BCC was reported (Beck *et al.*, 2008).	*TRPC1/4* Potential prognostic markers.
	TRPC6 Activation augmented cellular differentiation in actinic keratosis (*in situ* SCC) (Woelfle *et al.*, 2010).	*TRPC6* Activation might be beneficial.
Malignant melanoma	*TRPM1* Expression correlated inversely with the metastatic potential of skin melanomas (Deeds *et al.*, 2000; Duncan *et al.*, 2001; Miller *et al* 2004; Zhiqi *et al.*, 2004). miRNA211 coded in an intron of TRPM1 was shown to be responsible for the tumour-promoting effect of TRPM1 (Levy *et al.*, 2010; Mazar *et al.*, 2010; Boyle *et al.*, 2011; Guo *et al.*, 2012).	*TRPM1* Down-regulation might be a prognostic marker for metastasis (Deeds *et al.*, 2000; Duncan *et al.*, 2001; Miller *et al.*, 2004; Zhiqi *et al.*, 2004).
	TRPM2 Augmented susceptibility to apoptosis (Orfanelli *et al.*, 2008).	*TRPM2* Activation might be beneficial.
	TRPM8 Expression was increased (Tsavaler *et al.*, 2001). Activation induced Ca^{2+}-dependent cell death (Slominski, 2008; Yamamura *et al.*, 2008).	*TRPM8* Potential prognostic marker. Activation might be beneficial.
Skin ageing and UV-induced diseases	*TRPV1* It is involved in mediating the effect of UV exposure to induce inflammation and to up-regulate MMP-1 (Li *et al.*, 2007; Lee *et al.*, 2008b; 2009b; 2011). Increased expression was found in aged skin (Lee *et al.*, 2009a).	*TRPV1* Antagonisms might be beneficial. Antagonism inhibited UV-induced skin thickening, MMP and pro-inflammatory cytokine expression (Lee *et al.*, 2011).
DA	*TRPC1* It was found to be overexpressed and can contribute to pathomechanism via regulating Ca^{2+} influx (Barfield *et al.*, 2002; Pani *et al.*, 2006).	*TRPC1* Antagonisms might be beneficial.
OS	*TRPV3* Gain-of-function mutations were found to play a causal role in the disease (Lai-Cheong *et al.*, 2012; Lin *et al.*, 2012).	*TRPV3* Antagonisms or targeted gene therapy might be beneficial.

cutaneous non-melanoma cancers such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Indeed, BCC tissues practically do not express TRPC1 and TRPC4 (Beck *et al.*, 2008), which would explain the accelerated growth and defective differentiation of BCC-derived malignant cells. Furthermore, the induction of TRPC6-mediated Ca^{2+} influx by triterpenes in keratinocytes isolated from patients with actinic keratosis (*in situ* SCC) suppressed cell growth and evoked differentiation (Woelfle *et al.*, 2010).

Finally, Darier's disease (DAR), a genetic dermatosis, should also be mentioned. This autosomal dominant disorder, whose leading symptoms are the development of hyper- and dyskeratotic skin symptoms (papules), is caused by the mutation of the *atp2a2* gene encoding the SERCA2b endoplasmic reticulum Ca^{2+} pump (Alexander *et al.*, 2013d; Barfield *et al.*, 2002; Pani *et al.*, 2006). In cultured DAR keratinocytes, a highly augmented TRPC1-mediated Ca^{2+} influx is detected which results in an abnormal balance of the otherwise fine-tuned programs of differentiation, proliferation and apoptosis (Pani *et al.*, 2006); therefore, TRPC1 is most probably involved in the pathogenesis of DAR.

Concluding remarks

In this review, we summarized those recent findings that suggest cellular signalling mechanisms coupled to various TRP channels are not only involved in the sensory processing of, for example, cutaneous pain and itch, but also play significant roles in controlling the growth, differentiation and survival programmes of skin cells; the formation, maintenance and regeneration of the skin barrier and the cutaneous immune functions. Moreover, as summarized in Table 1, we have also presented (thus far rather preclinical and pilot)

evidence that multiple TRP channels may participate in the development of certain skin diseases. Therefore, we invite well-defined and sophisticated preclinical and clinical studies to uncover how TRP-targeted approaches can be exploited in the management of such highly prevalent skin conditions such as AD, acne vulgaris, psoriasis, cutaneous melanoma and non-melanoma cancers.

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Conflict of interest

None.

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