

TRPV3: a skinny channel

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| Journal: | <i>Experimental Dermatology</i> |
| Manuscript ID: | Draft |
| Manuscript Type: | Review Article |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Nilius, Bernd; KU Leuven, Department of Cellular and Molecular Medicine, Laboratory Ion Channel Research Biro, Tamas / Editorial Board Member; University of Debrecen, Physiology |
| Keywords: | transient receptor potential vanilloid-3, keratinocyte, proliferation, differentiation, skin diseases |
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TRPV3: a skinny channel

Bernd Nilius* and Tamás Bíró#

*KU Leuven, Department of Cellular and Molecular Medicine, Laboratory Ion Channel Research, Campus Gasthuisberg, Herestraat 49, bus 802, Leuven, Belgium

#DE-MTA “Lendület” Cellular Physiology Research Group, Department of Physiology, University of Debrecen, Medical and Health Science Center, Research Center for Molecular Medicine, Nagyterdei krt. 98., H-4032 Debrecen, Hungary

Correspondence to: Tamás Bíró (biro.tamas@med.unideb.hu)

Abstract

The skin is our largest organ serving different tasks from barrier formation through somatosensing to hair development. Recently, members of the large *trp* (Transient Receptor Potential, TRP) gene family encoding proteins which form cation selective ion channel have been identified to play a crucial role in skin functions. Within the 28 different mammalian TRP channels, TRPV3 might be the most prominent and important member in the skin. This review gives an overview on functional properties of TRPV3 in skin physiology and in certain skin diseases.

TRP channels: an introduction

In 1969, a *Drosophila* mutant was discovered which was defective in light sensing and exhibited only transient light-induced receptor potentials (TRP) instead the normal maintained response (1). This finding was explained by a defect in an ion channel and triggered the discovery of the *trp* gene family which encodes TRP channels (for the history of this discovery see (2-4)). The TRP channel superfamily contains 28 mammalian members (27 in human) subdivided in 6 subfamilies which all permeate cations (5, 6). TRP channels – which probably function mostly as hetero- or homo-tetramers (7, 8) (more detailed information see in [TRP channel data base Clapham/Owsianik/Nilius](#) (9)) – are located in the plasma membrane (PM) as Ca²⁺ entry pores and generate upon activation cell depolarization; this can result in activation or inactivation of voltage dependent ion channels thereby modulating the driving force of ion flux through channels and transporters. Some TRPs also act as intracellular ion channels, mainly as Ca²⁺ release channels, in several cell organelles such as lysosomes, endosomes, Golgi network, endoplasmic reticulum, and synaptic vesicles (10).

TRPV family

Members of the TRPV (vanilloid) family comprise 6 ion channels based on homology. Four groups can be identified: TRPV1/TRPV2, TRPV3, TRPV4, and TRPV5/6. This family is named after the first mammalian member of the TRPV subfamily, which binds vanilloids (e.g. capsaicin) and was first coined as vanilloid receptor-1 (VR1) (6, 11). Members of the TRPV family function as homo and/or heterotetrameric complexes but can also hetero-multimerize with other TRP channels such as TRPC1 and TRPP2 (7, 12, 13).

Among the TRPVs channels, TRPV1, 2, 3, and 4 have striking temperature sensitivities. Indeed, TRPV1 is activated at $>43^{\circ}\text{C}$; TRPV2 at $>52^{\circ}\text{C}$; TRPV3 at $>33^{\circ}\text{C}$; and TRPV4 at $>30^{\circ}\text{C}$ (14). These thermo-TRPVs are modestly permeable to Ca^{2+} whereas TRPV5 and TRPV6 are the only highly Ca^{2+} selective channels in the TRP family. Nevertheless, functions of all of these channels are tightly regulated by the intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) and phosphoinositides (15).

With respect to skin physiology and pathophysiology, probably TRPV3 is the most important TRPV channel. Therefore, the cutaneous role of TRPV3 will be detailed in this review.

TRPV3: a thermosensor?

TRPV3 ([ENST00000301365](#)), which shares 43% sequence similarity with the first identified TRPV1, was cloned by three groups (16-18). After its identification, it appeared as a surprise that this channel was not highly expressed in the sensory dorsal root (DRG) or trigeminal (TG) ganglia (at least in rodents). Instead, TRPV3 was found to be most abundantly expressed in the skin, especially in epidermal and hair follicle keratinocytes, as well as in the tongue, testis, cornea, the distal colon, human larynx, and inner ear (17-24).

TRPV3, expressed by mouse epidermal keratinocytes (or in heterologous expression systems) was found to be activated by innocuous warm temperatures above 33°C (16-18). Yet, the role of TRPV3 as a thermosensor is still not clearly understood. First, it was shown that TRPV3 knockout mice exhibit strong deficits in responses to innocuous and noxious heat but not in other sensory modalities (19). In addition, heating of cultured keratinocytes was found to cause ATP release which, in turn, activates sensory nerves fibers; this effect is also defective in TRPV3 knockout mice (25).

However, intragastric administration of natural TRPV3 agonists (thymol, ethyl vanillin) does not have any effect on thermogenesis or heat diffusion, indicating a restricted effects of TRPV3 on autonomic thermoregulation (26). In addition, a re-investigation of the TRPV3 knockout mice with defined backgrounds exhibited no obvious alterations in thermal preference behavior; it appears to be clear now that TRPV3 channels (similar to TRPV4, which is also highly expressed in epidermal keratinocytes) exhibit limited (if any) involvement in thermoregulation (27). In addition,

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3 it can also be speculated that there is a significant functional redundancy between TRPV1, 3, and
4 4; therefore, genetic deletion of e.g. *trpv3* might not result in significant thermosensory deficit on
5 the animals.
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8 Intriguingly, evolution seems to require a flexible temperature sensing of TRPV3. Important for
9 our understanding of TRPV3 is the fact that these channels in lower vertebrates (e.g. the western
10 clawed frog *Xenopus tropicalis*) do not respond to heat stimuli; instead, TRPV3 is activated by
11 cold. Therefore, frog skin TRPV3 channels likely detect noxious cold temperatures whereas
12 mammals detect such environmental temperatures which are suitable for their respective optimal
13 environmental temperature; this indicates substantial flexibility of the channel functions during
14 evolution (28). Interestingly, the super-cooling agent icilin was shown to inhibit TRPV3 at low
15 concentrations (29). This might have practical implications for boosting of cold sensations
16 detected by keratinocytes and free nerve endings in skin and administration in diseases with an
17 increased TRPV3 activity (see below).
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20 Finally, TRPV3 is also activated by infrared heat. This activation is considered to have beneficial
21 effects to treating metabolic syndrome, as obesity prone rats exposed to infrared light showed a
22 higher synthesis of pro-opiomelanocortin (POMC, an anorectic compound produced in the
23 hypoglossal nucleus and medial nucleus tractus solitarius), a lower TRPV3 expression, and a
24 highly significantly reduced food intake (30).
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32 **TRPV3: role in cutaneous (patho)physiology**

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34 Keratinocytes are one of the key cell types of the skin orchestrating a plethora of functions. No
35 wonder, therefore, that TRPV3 which is highly expressed by these cells are suggested to be
36 involved in numerous cutaneous regulatory mechanisms and phenomena (summarized in **Figure**
37 **1.**)
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40 **Skin barrier formation**

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42 In mice, TRPV3 (similar to TRPV1 and TRPV4) is involved in the formation and maintenance of
43 the physical-chemical skin barrier. Among the numerous growth factors implicated in the
44 formation of the epidermal barrier, TRPV3 forms a signaling complex with the receptor of
45 epidermal growth factor (EGFR) and transforming growth factor- α (TGF- α). Activation of EGFR
46 leads to increased TRPV3 channel activity, which in turn stimulates TGF- α release resulting in the
47 formation of the barrier (31). Consistent with these findings, genetic deletion of *trpv3* leads to
48 impaired epidermal barrier structure (31). In addition, temperature challenges which activate
49 TRPV3 (and TRPV4) accelerate barrier recovery after mechanical disruption (tape stripping of
50 back skin of mice) of the barrier (32). Yet, the human relevance of these findings is to be
51 determined.
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Hair growth

Interestingly, wavy hair phenotypes were detected in mice with naturally occurring loss-of-function mutations in the genes of TGF- α and EGFR (33). Consistently, overactivity of the TGF- α /EGFR signalplex results in hairless phenotypes and skin cancers (34). Since mice lacking the *trpv3* gene also exhibit similar, yet subtle, hair phenotypes (wavy hair coat, curly whiskers), the role of TRPV3 in hair morphogenesis and hair follicle cycling is suggested (31).

The first evidence that TRPV3 is involved in hair growth came from a mouse engineered as a model for Down-syndrome crossed with a hair-less mouse, DS-Nh (35). Intriguingly, in breeding studies involving DS-Nh and Nh mice, positional cloning approaches identified the Gly573Ser mutation of the *trpv3* gene as responsible for the spontaneous hairless phenotype in these animals, as well as in hairless WBN/Kob-Ht rats (36). Furthermore, levels of genes encoding keratin-associated protein 16-1, 16-3, and 16-9, representing the anagen phase of the hair follicle, were decreased in the skins of these mutant mice. Since the Gly573Ser mutation of TRPV3 were described as “gain-of-function” mutants with constitutive opening of the channels (37), it is proposed that regulation of TRPV3 is important for appropriate hair development in rodents (38).

Of great importance, TRPV3 apparently also controls human hair follicle growth and cycling. Activation of TRPV3 by natural or synthetic agonists in human scalp hair follicle organ-cultures was shown to inhibit hair shaft elongation, suppress intrafollicular proliferation, and induce premature, apoptosis-driven organ-involution (catagen) (20). Since functional TRPV3 channels were identified on cultured human hair follicle-derived outer root sheath keratinocytes, in which the activation of TRPV3 and the concomitant elevation of $[Ca^{2+}]_i$ resulted in the inhibition of cell growth and the onset of cell death (20), the above results collectively argue for the negative regulatory role of TRPV3 in the processes of hair growth (both in rodent and human).

Cutaneous growth and survival

TRPV3 also regulates growth and survival of interfollicular skin cell populations. TRPV3 (similar to TRPV1, 2, and 4) is probably involved in keratinocyte cell death after treatment at noxious temperatures at $\sim 60^\circ\text{C}$ as the nonselective TRPV blocker ruthenium red reduced the heat mediated thermal skin injury (39). Of further importance, TRPV3 also modulates intracutaneous nitric oxide (NO) synthesis which is independent from NO synthase (NOS) enzymes. NO production in the skin, which is a hypoxic tissue enriched in nitrites, plays important roles in wound healing and other biological processes (reviewed in (40)). TRPV3 activation induces NO production (and concomitant stimulation of keratinocyte migration and wound healing) via a nitrite-dependent pathway bypassing NOS, a mechanisms which is probably due to a proton-mediated nitrite-reduction. Since TRPV3 is also activated by protons, the effect of required low pH is most probably mediated by TRPV3 activation (41).

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3 As a further support for the “proton connection”, the proton-donor α -hydroxyl acids (AHAs) from
4 natural sources also seem to activate TRPV3. Topically applied AHAs, which exhibit strong
5 intracutaneous penetration, are widely used in the cosmetic industry as part of formulations which
6 induce chemical peeling (exfoliation of the str. corneum) and hence improve skin maintenance
7 and turnover. Among the AHAs, the intracellular acidification evoked by glycolic acid induced
8 cellular death of human epidermal HaCaT keratinocytes by the activation of TRPV3 (42). It can
9 be postulated therefore that activation of TRPV3 by intracellular protons and cell death in
10 keratinocytes is the molecular basis for the cosmetic use of AHAs and their therapeutic potential
11 in acidic pH-related skin disorders.
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17 **Skin inflammation**

18 The “gain-of-function” (Gly573Ser) mutation of the *trpv3* gene not only results in a hairless
19 phenotype but, albeit at much lower penetrance, also a spontaneously developing dermatitis
20 which resembles to characteristics of one of the most prevalent inflammatory skin conditions, i.e.
21 atopic dermatitis (AD) (36) (37). Of further importance, transgenic overexpression of the
22 TRPV3^{Gly573Ser} channels in keratinocytes of mice also results in such skin (inflammation,
23 hyperkeratosis, pruritus, immune cell infiltration, elevated cutaneous nerve growth factor [NGF]
24 expression) and systemic (increased plasma IgE and pro-inflammatory cytokines) symptoms
25 which highly resemble to those of human AD (43). Interestingly, in a genetic study, it was shown
26 that the Gly573Ser mutation contributes to the development of hapten-induced but not of
27 spontaneous dermatitis (44).
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34 Furthermore, agonist (eugenol, 2-aminoethoxydiphenyl borate) or heat stimulations of TRPV3
35 expressed by cultured keratinocytes induce the release of the pro-inflammatory interleukin IL-1 α
36 and prostaglandin E2 (PGE₂) (45, 46). Intriguingly, as an “other way around” effect, numerous
37 endogenous pro-inflammatory agents (such as bradykinin, PGE₂, histamine, ATP, receptor-
38 coupled hydrolysis of phosphatidylinositol 4,5-bisphosphate and activation of protein kinase C ϵ)
39 are able to sensitize TRPV3 to warm temperatures (46-48) resulting in an autocatalytic, TRPV3-
40 mediated augmentation of cutaneous inflammation and the development of such related
41 symptoms as e.g. thermal hyperalgesia (see also below).
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47 The pro-inflammatory role of TRPV3 is also suggested by investigating the cutaneous effects of
48 resolvins, a group anti-inflammatory and pro-resolving molecules generated endogenously by ω -3
49 lipid metabolism. Of great importance, 17(R)-resolvin D1 (17R-RvD1), a naturally occurring pro-
50 resolving lipid, was shown to specifically inhibit TRPV3 expressed by cultured epidermal
51 keratinocytes at nanomolar concentrations (49).
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3 Finally, it is noteworthy that in rosacea, a frequent chronic inflammatory skin disease, a dramatic
4 up-regulation of TRPV3 is found (50) which further supports the role of TRPV3 as an important
5 channel in the skin inflammation.
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8 **Cutaneous pain**

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10 Although the thermosensory role of TRPV3 is uncertain (see above), the TRPV3 channels
11 expressed by epidermal keratinocytes seem to participate in processing other sensory modalities
12 such as pain and itch.
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15 With respect to pain sensation, it is noteworthy that the naturally occurring monoterpenoid TRPV3
16 agonists (e.g. camphor, eugenol, carvacrol, etc.) are recognized skin sensitizers and, when
17 applied topically, they induce various degrees of irritations and pain (45, 51). Yet, genetic studies
18 using TRPV3-deficient mice have resulted in conflicting data (similar to as described for
19 thermosensation, see above). This might be due to, at least in part, that the (usually low)
20 expression of TRPV3 in mouse sensory ganglia, where the soma of the sensory afferents is
21 located, exhibits a significant species-dependence (27) .
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26 However, increasing body of evidence suggests that keratinocytes, as “first line nociceptive
27 transducers” (reviewed in (52)), play a crucial role in cutaneous nociception via their TRPV3-
28 coupled signaling mechanisms. Indeed, using transgenic mice overexpressing TRPV3 exclusively
29 in epidermal keratinocytes, it was shown that keratinocytes participate in thermal pain
30 transduction; namely, TRPV3 activation of these cells results in the release of the pro-
31 inflammatory (see above) and algogenic intercellular messenger PGE₂ which, in turn, stimulates
32 the adjacent sensory afferents (46). It addition, it was also suggested that TRPV3-mediated
33 release of NO from keratinocytes not only promotes keratinocyte migration and wound healing
34 but also induce pain, most probably by stimulating “pain-inducing” TRP channels, i.e. TRPV1
35 and/or TRPA1, which are reportedly expressed at the cutaneous sensory termini (41). Finally,
36 TRPV3 stimulation of keratinocytes was also shown to result in the release of another algogenic
37 substance ATP (25); therefore, ATP could also be listed among the keratinocyte-derived
38 candidate nociceptive messenger molecules.
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46 A further support for the nociceptive role of keratinocyte-expressed TRPV3 arises from using
47 endogenous TRPV3 modulators. Farnesyl pyrophosphate (FPP), an endogenous algogenic
48 substance, produced in the mevalonate pathway, was found to specifically activate TRPV3 on
49 cultured keratinocytes. Interestingly, an anti-nociceptive endogenous isopentenyl pyrophosphate
50 (IPP), an upstream metabolite in the same pathway, is an inhibitor of the keratinocyte-TRPV3 (53,
51 54). In a mouse inflammatory pain model (intradermal administration of complete Freund's
52 adjuvant), both IPP and 17R-RvD1 (the anti-inflammatory endogenous TRPV3 inhibitor, see
53 above) effectively inhibited inflammatory pain whereas FPP induced acute irritative behavior (53,
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3 54). Of greatest importance, shRNA-mediated silencing of TRPV3 in epidermal keratinocyte
4 markedly abrogated these effects (49, 54).
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7 Finally, it should be mentioned that new small molecule inhibitors of TRPV3 have clearly shown
8 analgesic effects in various inflammatory and non-inflammatory (thermal, chemical) pain models.
9 Of further importance, certain TRPV3 antagonists are now in clinical phase I and II as potent
10 analgesic agents (reviewed in (55, 56)). Therefore, although there are numerous opened
11 questions on how TRPV3 – expressed by epidermal keratinocytes and on human (!) DRG
12 neurons (57) – is molecularly involved in nociception in humans, TRPV3 is apparently a novel,
13 promising target for analgesic therapeutic approaches.
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17 **Pruriceptive itch**

18 Pruriceptive pruritus (i.e. skin-derived itch) is one of the most prevalent symptoms in Dermatology
19 practice. Due to extensive research efforts of the past decade, it is confirmed that the
20 pathogenesis of cutaneous itch involves the activation of a complex, multi-directional, self-
21 augmenting network. The cellular and humoral components of this network includes various non-
22 neuronal skin cells (e.g. epidermal keratinocytes, mast cells), pruriceptive sensory afferents, and
23 the plethora of pruritogenic soluble mediators which can be released from practically all cell types
24 of the skin upon itch-inducing insults (see reviewed in (58-60)). Apparently, similar to its role in
25 nociception, TRPV3 channels expressed by keratinocytes also participate in the “vicious circle” of
26 itch development and sensation.
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33 Indeed, the previously detailed “gain-of-function” (Gly573Ser) mutation of the *trpv3* gene in mice
34 not only results in a hairless phenotype and dermatitis but also severe itching (36, 37). Likewise,
35 the transgenic mice overexpressing the mutant TRPV3^{Gly573Ser} in the epidermal keratinocytes
36 includes, among others, itching/scratching behavior and the intracutaneous accumulation of NGF,
37 a highly effective pruritogenic substance (43). Perfectly in line with these data, in an
38 experimentally induced itch model (application of acetone-ether-water resulting in dry skin
39 conditions), TRPV3 KO mice exhibited significantly less intense scratching behavior than their
40 wild-type littermates, which is most probably due to a decreased sprouting of intracutaneous
41 sensory fibers of the mutant animals (61).
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47 Experimentally induced magnesium deficiency in mice or rats is widely used to model AD-like
48 robust scratching behavior (62, 63). Intriguingly, both extra- and intracellular magnesium was
49 shown to tonically inhibit TRPV3 activity in cultured epidermal keratinocytes (64). Therefore, it is
50 postulated that hypomagnesemia (which may develop in various human conditions such as e.g.
51 type 2 diabetes mellitus) may induce an “acquired gain-of-function” of TRPV3 resulting in the
52 development of pruritus.
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3 Finally, it is noteworthy all mediators either released upon TRPV3 stimulation from keratinocytes
4 (IL-1 α , ATP, PGE₂) or those which induce TRPV3 sensitization (e.g. bradykinin, PGE₂, histamine,
5 ATP) (45-48) are recognized pruritogenic agents. Since these factors, via the TRPV3-coupled
6 (and possibly other) signaling mechanisms, may further augment the release of one another from
7 skin cells, their functions additionally support the role of TRPV3 in itch.
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10 11 **TRPV3 channelopathy: Olmsted syndrome**

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13 In the past few years, several hereditary diseases, caused by defects in certain TRP genes, have
14 been described and many comprehensive reviews has been published (5, 65-67). Hereditary
15 channelopathies, i.e. mutations in the gene encoding the given channel resulting in channel
16 dysfunction, has gained an increasing interest lately since they very often provide surprising
17 insights to the functions of the channel and thereby identify novel pharmaceutical targets (55). As
18 only TRPV3 is considered here, we refer for more detailed information on channelopathies to use
19 the [OMIM](#) (68) search.
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23 As mentioned above, two “gain-of-function” mutations of the *trpv* gene at a single site cause an
24 autosomal dominant hairless phenotype with itchy dermatitis in mice (36). Intriguingly, an identical
25 “gain-of-function” mutation of *trpv* was described in Olmsted syndrome (OS, OMIM [607066](#) (69))
26 (also known as “Mutilating palmoplantar keratoderma with periorificial keratotic plaques” or
27 “Polykeratosis of Touraine”). Besides this Gly573Ser mutation, two other mutations (Gly573Cys
28 and Trp692Gly) have also been identified as “gain-of-function” channels and are also present in
29 OS (70, 71); Gly573Ser is probably a recurrent abnormality.
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33 OS is a rare genodermatosis; actually, it is sometimes difficult to diagnose because of clinical
34 overlap with other disorders and its uncertain mode of inheritance. Of great importance, the
35 characteristic symptoms of OS (the first “truly cutaneous TRPpathy”) provide an “ultimate proof”
36 for the aforementioned concept that TRPV3 channels, mostly expressed by keratinocytes, play
37 essential roles in epidermal proliferation, differentiation, survival, hair growth, and the
38 development of itch sensation. Indeed, OS is characterized by the combination of periorificial,
39 keratotic plaques, bilateral palmoplantar and periorificial keratodermas (which is most probably
40 due to the highly elevated, TRPV3-mediated apoptosis of keratinocytes and the concomitant
41 acceleration of epidermal turnover leading to hyperkeratosis), profuse alopecia, and severe
42 itching (**Figure 2.**)
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51 **Conclusions**

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53 In this review, we have described some biophysical properties of the vanilloid TRP channel,
54 TRPV3, which is the dominant TRP molecule in the skin. Although we know quite a number of
55 details on the molecular biology of this channel and its modulation, its striking involvement in skin
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(patho)physiology is not completely understood. Importantly, as we have shown above (see also **Figure 1**), TRPV3 is involved in the control of proliferation and survival of both interfollicular and hair follicle keratinocytes and thereby regulates epidermal, and adnexal growth. Moreover, TRPV3 mediates skin inflammation, cutaneous pain, and itch. Of further importance, its mutation causes the first identified TRPV3-channelopathy, the OS. Importantly, pathophysiological interference of TRPV3 in the skin and the dramatic defects in OS require mutant channels exhibiting a “gain-of-function” phenotype. This is reminiscent for the “gain-of-function” mutants of TRPV4 causing a plethora of bone diseases and neuropathies, such as e.g. Charcot-Marie-Tooth disease type 2 (reviewed in (72)).

The introduced experimental data as well as the mutant human (and mouse) phenotypes strongly suggest that **TRPV3 antagonists** might be useful tools in the management of a wide array of skin diseases. In **Table 1**, we mention a few dermatoses in which the beneficial effects of inhibiting TRPV3 activity could be predicted. Evidently, although the presented intriguing findings certainly hint to a “more than skinny” perspective of TRPV3 as a therapeutic target in Dermatology, further extensive in vitro and in vivo studies are required to unambiguously prove the applicability of these agents. Therefore, to contribute to these efforts, we close our review by defining a few “research frontiers” for experimental and clinical Dermatologists.

- ✓ From the therapeutic perspective, possibly the most important goal is to identify the putative alterations in the expression and function of TRPV3 in human skin diseases (including, yet not limited to, those listed in **Table 1**).
- ✓ Furthermore, it is also desired to determine of the expression and functionality of TRPV3 in various (non-keratinocyte) cell populations of the human skin including e.g. adnexal cells, resident and infiltrating immune cells, etc.
- ✓ Intriguingly, although the role of TRPV3 in controlling growth and survival of epidermal keratinocytes is presented in numerous studies, its involvement in the establishment, maintenance, and regeneration of the *human* epidermal skin barrier is still not defined. Since pathological barrier functions are unambiguously attributed to the development and/or progression of such highly prevalent “barrier diseases” as e.g. AD, psoriasis, dry skin condition, etc. (73-75) human studies are now urgently needed to uncover the effects of manipulating TRPV3 activity on the complex cutaneous barrier functions.
- ✓ In contrast to our knowledge on the biophysical, biochemical, and molecular properties of TRPV3, we possess only very limited data on the downstream signaling events following its activation in cutaneous cells. Therefore, complex and systematic studies are warranted to define the TRPV3-coupled intracellular and/or intranuclear signaling pathways and the effect of TRPV3-acting agents on the global gene expression profiles of the target cells.

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3 ✓ Finally, since numerous other TRPs are also expressed by various cutaneous cells, it
4 also is of great importance to define the interplay of TRPV3 with other TRP channels,
5 both at the cellular/molecular and the intercellular levels.
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8 9 **Acknowledgement**

10 For T.B., the writing of this review was supported by Hungarian (“Lendület” LP2011-003, TÁMOP-
11 4.2.2./A-11/1/KONV-2012-0025, OTKA 78398, OTKA 101761) and EU (FP7-REGPOT-2008-
12 1/229920) research grants. B.N. thanks all members of the Laboratory of Ion Channel Research,
13 KU Leuven, for always helpful discussions and support. Authors acknowledge the driving force
14 and encouragement of Ralf Paus to write this review and the technical help of Attila G. Szöllösi in
15 the preparation of the manuscript.
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20 21 **Figure legends**

22 *Figure 1. The central role of TRPV3 in the regulation of multiple cutaneous functions*

23 TRPV3, expressed by epidermal and hair follicle keratinocytes, can be activated and/or sensitized
24 by various exogenous agents (e.g. botanical terpenoids, α -hydroxyl acids), endogenous
25 substances (e.g. 17(R)-resolvin D1, farnesyl pyrophosphate), sensory stimuli (e.g. heat) and
26 intracellular signaling pathways which are coupled to 7TM or 1TM receptors. These stimuli induce
27 a TRPV3-mediated influx of Ca^{2+} to the keratinocytes which, by initiating mostly unidentified
28 downstream mechanisms, results in dual effects. i) As **direct effects**, TRPV3 stimulation inhibits
29 proliferation of keratinocytes, induces cellular apoptosis, and modulates epidermal differentiation
30 and, via these processes, was implicated in the regulation of hair growth and barrier functions.
31 ii) In parallel, as **indirect effects**, activation of TRPV3 on keratinocytes results in the release of
32 numerous agents (e.g. ATP, prostaglandin E_2 , nitric oxide). These “intercellular messengers” may
33 then activate neighboring cutaneous cells and initiate the onset of such mechanisms as e.g.
34 various sensory phenomena (pain and itch, via the stimulation of specific sensory afferents) and
35 cutaneous inflammation (via the activation and recruitment of cellular and humoral components of
36 the skin immune system).
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46 *Figure 2. Characteristic symptoms of Omsted syndrome*

47 **A)** “Gain-of-function” mutations of the *trpv3* gene, described in Olmsted syndrome (OS) patients,
48 resulting in a constitutive opening of the TRPV3 channel expressed by keratinocytes. **B-D)**
49 Characteristic skin phenotype of OS: bilateral mutilating palmoplantar keratoderma (**B**);
50 periorificial keratotic plaques (**C**); and diffuse hair loss with follicular papules (**D**). Reprinted with
51 permission from (70).
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Tables

Table 1. Possible use of TRPV3 inhibitors in skin diseases

| Disease | Cutaneous target cell | Expected beneficial effects |
|---------------------------------------|----------------------------------|---|
| Psoriasis | Keratinocytes | Anti-proliferative and anti-inflammatory effects (suppression of keratinocyte hyperproliferation; inhibition of release of pro-inflammatory mediators) |
| Skin tumors | Transformed skin cells | Anti-proliferative effects (suppression of highly accelerated cell growth; induction of apoptosis) |
| Unwanted hair growth (e.g. hirsutism) | Hair follicle epithelial cells | Induction of hair loss (inhibition of hair shaft elongation and follicular keratinocyte proliferation; acceleration of premature organ involution catagen) |
| Pain | Keratinocytes, sensory afferents | Analgesic effects (inhibition of release of algogenic mediators from keratinocytes; inhibition of nociceptive sensory neuron activity) |
| Itch | Keratinocytes, sensory afferents | Anti-pruritic effects (inhibition of release of pruritogenic mediators from keratinocytes; inhibition of pruriceptive sensory neuron activity) |
| Atopic dermatitis | Keratinocytes | Anti-inflammatory and anti-pruritic effects (inhibition of release of pro-inflammatory and pruritogenic mediators from keratinocytes; inhibition of pruriceptive sensory neuron activity) |
| Other dermatitis types | Keratinocytes | Anti-inflammatory effects (inhibition of release of pro-inflammatory mediators) |
| Rosacea | Keratinocytes | Anti-inflammatory effects (inhibition of release of pro-inflammatory mediators) |
| Acne vulgaris | Keratinocytes | Anti-proliferative and anti-inflammatory effects (inhibition of infundibular keratinocyte hyperproliferation; inhibition of release of pro-inflammatory mediators) |

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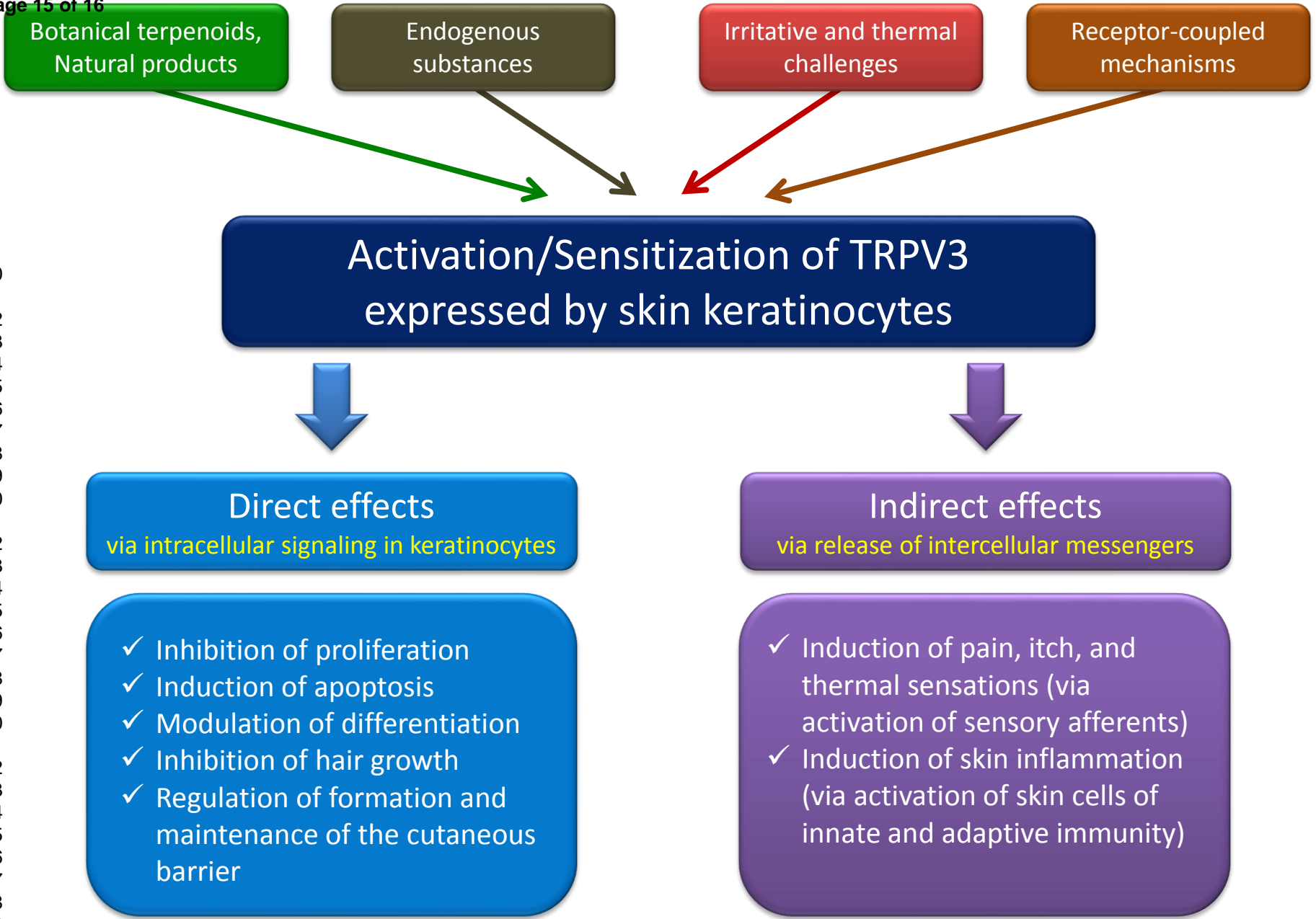
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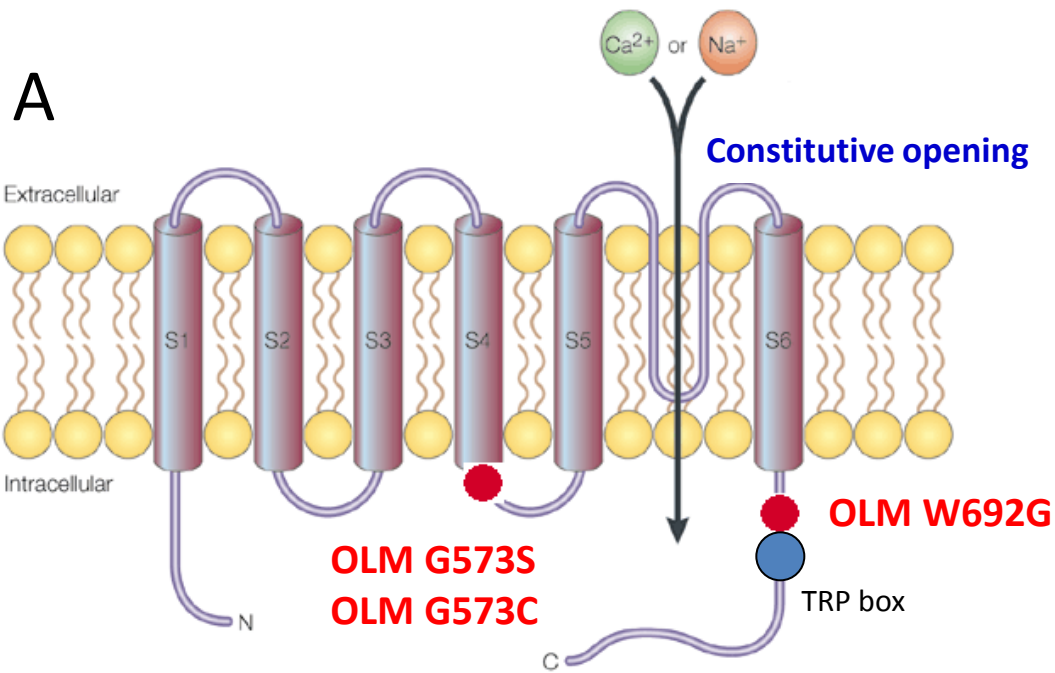
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Nilius & Bíró: Figure 1



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Nilius & Bíró: Figure 2