We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

5,800
Open access books available

142,000
International authors and editors

180M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Hot on the Trail of Skin Inflammation: Focus on TRPV1/TRPV3 Channels in Psoriasis

*Lisa S. Martin, Emma Fraillon, Fabien P. Chevalier
and Bérengère Fromy*

Abstract

Transient Receptor Potential Vanilloid (TRPV) channels are expressed in various skin cells, including non-neuronal cell types such as epidermal keratinocytes. They are polymodal sensors of the environment, regulating physiological function in response to a wide variety of stimuli. Indeed, in addition to their significant role in thermal responses and thermoregulation, TRPV channels are also implicated in local skin inflammation processes. Thus, these calcium permeable channels are associated to multiples skin diseases with inflammation, such as atopic dermatitis or psoriasis. In this chapter, we will mainly focus on TRPV1 and TRPV3 channels, as emerging pivotal targets for maintaining skin homeostasis in psoriasis-related inflammation.

Keywords: skin, epidermis, TRPV1, TRPV3, calcium channel, inflammation, psoriasis

1. Introduction

Skin is the largest organ of human organism, approximately 2m^2. This envelop, in constant contact with the environment, can be divided into three layers: a deep layer, the hypodermis; then an intermediate layer, the dermis; and finally, a superficial layer, the epidermis. This top layer is mainly constituted of keratinocytes, which form the first physical and chemical barrier between the external environment and our body. To maintain this function, keratinocytes undergo a multistep process of differentiation, from proliferating cells of the *stratum basale* to *stratum spinosum* (mature basal cells linked by keratin filaments – desmosomes), *granulosum* (mature keratinocytes, which generate keratin and keratohyalin granules), and *lucidum* (dead and flattened cells), to finally generate dead cornified corneocytes found in *stratum corneum* [1, 2]. These highly differentiated cells, devoid of nucleus and organelles, form the cornified envelop and are essential for the skin barrier function.

Despite its major keratinocyte content, epidermis is also composed of other cell populations in order to ensure protection of our organisms [1, 2]. Its immunity is guaranteed by Langerhans cells, a dendritic cell that contributes to innate and

adaptative immunity [1, 2]. The sensory nerve endings passing through the epidermis (C-fibers and Aδ-fibers) were thought to be the exclusive transducers for the detection of environmental factors such as heat and pain, but Merkel cells can also act as mechanosensors [3]. Free intra-epidermal sensory nerve endings are all unmyelinated: C-fibers are unmyelinated, while Aδ-fibers lose their myelination when they enter the epidermis, allowing them to come into direct contact with the epidermal keratinocytes (**Figure 1A**) [4]. Therefore, in addition to the intra-epidermal sensory nerve endings, the epidermal keratinocytes also function as a sensory hub, able to detect environmental changes [5, 6]. Finally, the epidermis is constituted by another cell population: the melanocytes, located in the basal layer. With one for 4–10 keratinocytes, melanocytes provide a barrier from ultraviolet (UV) thanks to their ability to produce melanin, a photoprotector pigment [1, 2]. Opposite to the epidermis, the
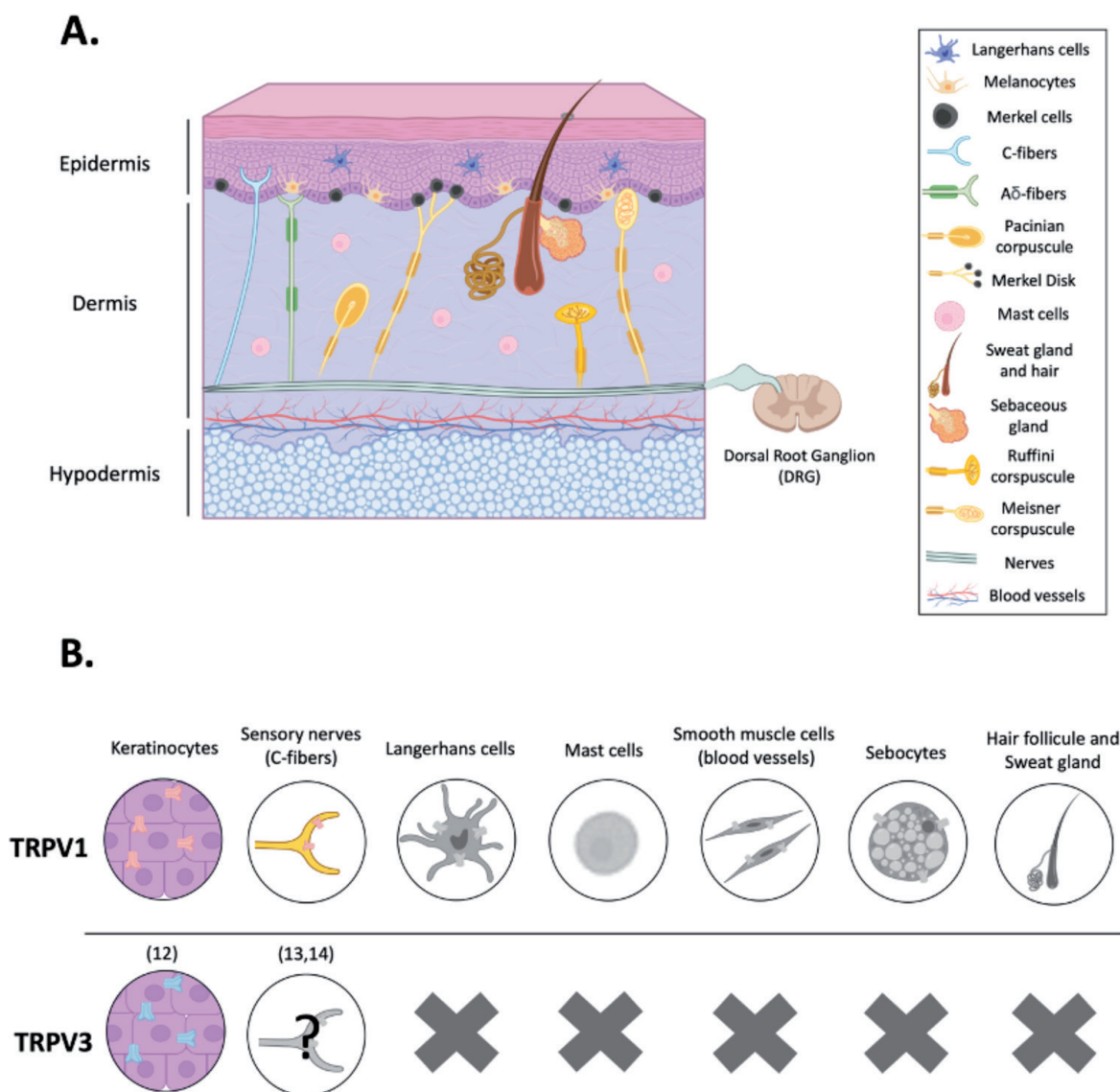

Figure 1.
Schematic representation of skin and TRPV1/TRPV3 location. A. Skin structure. Skin and its three layers: epidermis, dermis, and hypodermis. Nerve fibers are present in the epidermis or in the dermis depending on their properties and their type. Two major groups of skin nerve fibers are represented: Aδ fibers (green) poorly myelinated and able to pass through the dermo-epidermal junction, and Aβ fibers (yellow) strongly myelinated and not able to reach the epidermis. C-fibers are unmyelinated and able to pass through the dermo-epidermal junction. B. TRPV1 and TRPV3 location. TRPV1 is expressed in various cell types with a dominance in keratinocytes and sensory nerves (C fibers). TRPV3 expression is restricted to keratinocytes with a putative expression on sensory nerves.

dermis is mainly composed of extracellular matrix produced by dermal fibroblasts. This intermediate layer also supports dermal blood vessels, nerve fibers, and epidermal appendages (pilosebaceous unit and sweat glands). Finally, hypodermis is composed of adipocytes separated by connective tissue. This deep layer insulates and protects the skin from mechanical injuries [1, 2]. Thus, the skin allows a protection against externals insults (ultraviolet, pathogens, mechanical pressure, etc....) but also contributes to the maintenance of homeostasis such as information transfer, vitamin and metabolites secretions, hydric and thermal regulation.

To cope with various externals constrains, various cells of the skin express transmembrane sensors called Transient Receptor Potential (TRP) channels, which are involved in thermosensation, chemosensation, nociception, and mechanosensation [7]. TRP channels can be divided into six subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), and TRPV (vanilloid). Although TRPV channels have a major role in thermosensation [8], they also contribute to keratinocyte differentiation, skin barrier formation, and permeability thanks to calcium regulation. However, it appears that an aberrant TRP channel expression and function might contribute to some skin inflammatory diseases. In this review, we will focus on TRPV1 and TRPV3 structures, activation mechanisms, and their physiological roles in skin. We will also provide a new approach to study TRPV1 and TRPV3 channels in a very common chronic inflammatory disease, such as psoriasis.

2. TRPV1 and TRPV3 structure and gating

2.1 Expression and genetics

Among the six members of TRPV channels, thermosensors TRPV1 and TRPV3 are calcium channel both highly expressed in the skin, with different cells types expression (**Figure 1B**). The TRPV1 channel was firstly described on nociceptive sensory nerves from Dorsal Root sensory Ganglia (DRG) by Caterina *et al* in 1997 [9]. TRPV1 was detected on a subset of skin sensory nerves, such as peptidergic and non-peptidergic C fibers. Different studies have also proposed TRPV1 channel to be expressed on non-neuronal skin cells population. Indeed TRPV1 is expressed in human and mouse skin as TRPV1 immunoreactivity has been observed on Langerhans cells, mast cells, endothelium, and smooth muscle cells from dermal blood vessels, differentiated sebocytes, sweat glands, hair follicles (inner root and infundibulum), and finally on keratinocytes [10–12].

Unlike TRPV1, TRPV3 channels tissue expression is more restricted. Peier *et al.* (2002) have demonstrated the expression of Trpv3 in the skin, with a strong immunodetection on keratinocytes from epidermis and hair of rat [13]. We also confirmed a higher *TRPV3* expression in cultured human primary keratinocytes as compared with *TRPV1* (5.5-fold change, unpublished data). In contrast, *TRPV3* expression and activity on sensory nerves are still controversial. Indeed, *TRPV3* mRNA was detected on sensory neuron in DRG and trigeminal ganglia of monkey [14], while others have reported an absence of Trpv3 activity on mouse DRG, and then suggested no expression on these cells [15]. Finally, another group has proposed a heterodimeric form TRPV1-TRPV3 on sensory neurons [16]. Even if TRPV3 expression on sensory nerves is not completely clear, it is believed that epidermal TRPV3 and sensory nerves are able to communicate via chemical mediators. Indeed, TRPV3 activation in keratinocytes causes the secretion of an array of signaling factors, such as Nerve Growth Factor (NGF), Nitric Oxide (NO), Prostaglandin E2 (PGE_2), and Adenosine-Triphosphate (ATP).

TRPV1 (chr17:3,565,446-3,609,411) and TRPV3 (chr17:3,513,190-3,557,805) genes exist in tandem on human chromosome 17, with the same transcriptional orientation and are distant from less than 7650 base pairs, indicative of an ancestral gene duplication. In humans, the TRPV1 gene spans 17 exons encoding an 839 amino acids (aa) protein. Alternative splicing may occur and give rise to a modified amino acids sequence in the first 150 residues. The TRPV3 gene spans 18 exons encoding a prevalent isoform of 790 amino acids. As for TRPV1, TRPV3 might be differentially spliced, yielding two additional isoforms of 791 (additional A in position 760) and 765 amino acids (peptide sequence at 760–765 modified from DFNKIQ to GTVAVR together with deletion of residues 766–790). The most prevalent forms of TRPV3 (790 aa) and TRPV1 (839 aa) share 43% sequence homology.

2.2 Common features

The TRP superfamily is the second largest class of ions channels with a voltage-dependent activation mechanism. However, TRP members not only respond to electric signal but are also able to sense several environmental stimuli, rendering them polymodal sensors of the environment. These channels share a highly conserved protein architecture and require a tetrameric assembly to generate a functional central cation permeation pore. Apart from this ion channel pore, different subdomains of the TRPV proteins are responsible for their ability to be responsive to various environmental signals. Each subunit of the tetrameric complex is composed of six transmembrane
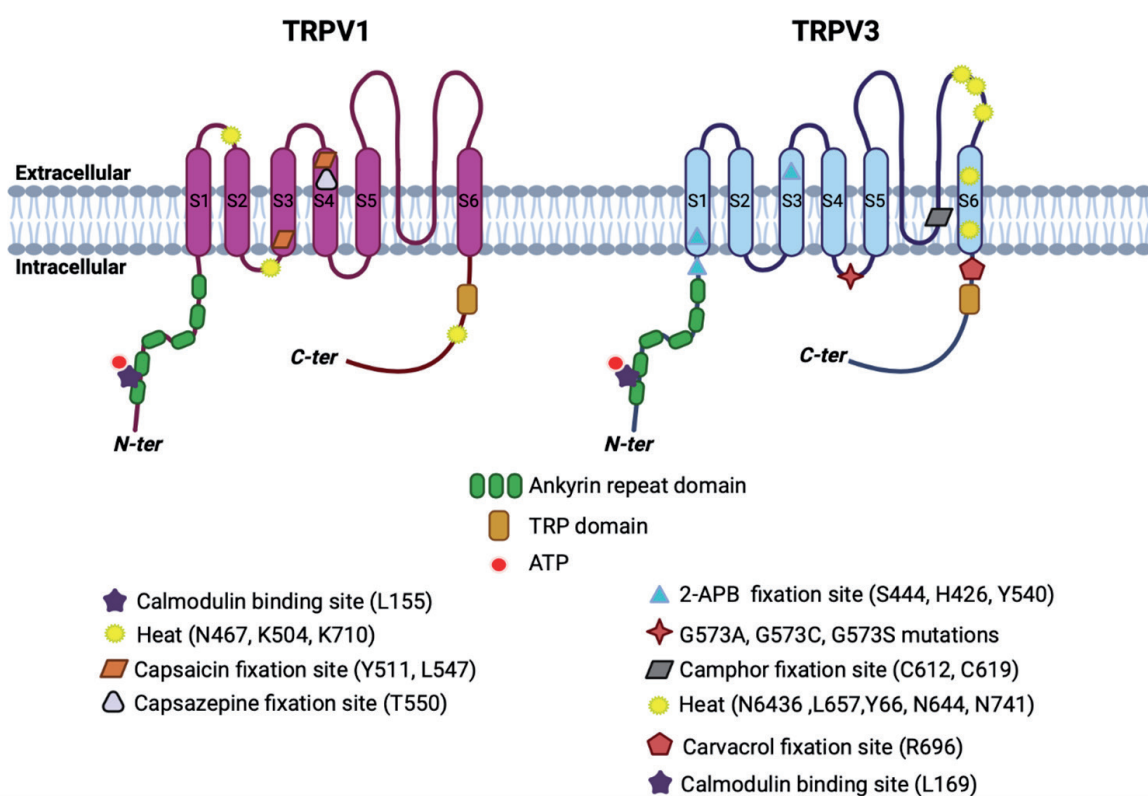

Figure 2.
TRPV1 and TRPV3 structure. Left – Highlighting the fixation sites of TRPV1 activators (heat, capsaicin) and interacting protein (calmodulin). Right – Fixation sites of TRPV3 activators (2-APB, carvacrol, camphor, heat), interacting protein (calmodulin) and mutations involved in the establishment of the inflammatory response (G573A, G573C, G573S). Ankyrin repeat domain and TRP domain are conserved in TRPV1 and TRPV3 structures.

segments (S1–S6), with the cation permeable pore formed by a reentrant loop located between S5 and S6 (**Figure 2**). The S1–S4 bundle likely forms the voltage sensor module, although TRPV1 and TRPV3 exhibit a weak voltage dependence for gating. This relatively low capacity of TRPV channels to respond to electric current may be due to the scarcity of positively charged amino acids in the S4 domain that contains a single arginine residue [17, 18]. The large cytoplasmic N-terminal part of a monomer comprises six ankyrin repeats, each consisting of a 33-residue motif forming two antiparallel alpha helices separated by loops linking the adjacent repeats. The ankyrin repeat domains (ARDs) are highly conserved in TRPV1 and TRPV3. The C-terminal part is also a large intracellular region containing a TRP-domain, another highly conserved distinctive and fundamental feature of TRP channels, consisting of a 25 amino acids α-helix structure with a conserved sequence IWKLQR called the TRP box. This TRP domain is running parallel to the inner plasma membrane and intimately lodged within the intracellular side of the S1–S4 module [19, 20]. A coiled-coil motif comprising residues of E684–R721 and overlapping with the TRP domain in the C-terminus of TRPV1 has been identified as an association domain and appears to be the molecular determinant of tetramerization [21]. In TRPV3, the C-terminal domain additionally forms a loop of 19 residues from V737 to V756, which has not been observed in other TRPV channels. This unique C-terminal loop domain extends along the TRPV3 intracellular skirt and forms an extensive network of interactions with ankyrin repeats 2–5 of the ARD [22]. Among all of these domains, several regions and specific residues have been mapped within TRPV1 and TRPV3 to regulate the channel gating. Indeed, heat, voltage, and ligand stimuli are sensed by TRPV channels by different structural domains.

2.3 Pore module

Both pores of TRPV1 and TRPV3 are prone to dilatation during stimulation, rendering them permeable for large cations [19, 23]. Thus, TRPV1 and TRPV3 are cation-selective channels exhibiting a notable preference for divalent cations, with the following permeability sequence: $Ca^{2+} > Mg^{2+} > Na+ \approx K+$. As for all TRPV channels, negatively charged amino acids in the pore play a central role in cation permeation, and furthermore, the opened pore is blocked by both extra- and intracellular cations. The S5-S6 segments are forming the central pore and the lower gate. This lower gate is formed by a hydrophobic seal, blocking permeation by hydrated ions when the channels are in their closed state. This hydrophobic seal is ensured by the critical residue I679 on S6 for TRPV1 and M677 on S6 for TRPV3 [20, 22]. An additional upper gate is formed by a short loop and helix between S5 and S6, called the pore helix (PH), and acts as a selectivity filter. TRPV1 displays a prolonged loop of 23 residues between S5 and the PH, named the pore turret. This pore turret is a mandatory structural domain for conformational rearrangements during heat activation of the TRPV1 channel, but is not part of the capsaicin agonist activation pathway [24, 25]. In TRPV3, the three key amino acids I644, N647, and Y661 located in the S6 are responsible for heat activation of the channel, since single-point mutants of these generate total loss of temperature activation, without affecting the overall TRPV3 structure [26]. Interestingly, the temperature sensitivity of the TRPV1 channel also implies the C-terminal domain [27].

2.4 Ligands

TRPV1 can be activated by numerous exogenous agonists including capsaicin, plant toxin resiniferatoxin (RTX), natural substances such as capsaicin-related

compounds from peppers, aromatic components, and animal vanillotoxins from the venom of the tarantula [28, 29]. For TRPV1, the three amino acids R491, Y511, and S512 in the S3 transmembrane segment are responsible for capsaicin sensitivity, while the region between S481 and T550 is responsible for binding of the antagonist capsazepine, without affecting the temperature activation [30, 31]. Natural substances also activate TRPV3, including camphor (C612 and C619), carvacrol, thymol, and eugenol [32]. Moreover, TRPV3 can be activated by synthetic molecules such as the well-documented 2-Aminoethoxydiphenyl Borate (2-APB).

2-APB is a common activator ligand of TRPV1 and TRPV3 channels [27]. In TRPV3, several transmembrane segments are implicated in the binding of the agonist 2-APB. In fact, there are three different sites of 2-APB fixation in TRPV3. A first site of fixation is involving S444 of S1, E501 and W493 of S2, and Y565, H523, and F526 of S3 that establish complementary interactions with different atoms of 2-APB [22]. A second site of 2-APB binding is mostly mediated by polar residues, such as H417 and T421 of the linker domain, H426 and H430 of the pre-S1 helix, and R693 and R696 of the TRP domain. Interestingly, the mutation H426A completely abolishes TRPV3 activation by 2-APB but not by camphor neither by carvacrol [22, 33, 34]. However, the residue R696 in the TRP domain appears critical in TRVP3 activation by external ligands since the mutation R696K abolishes 2-APB- and carvacrol-induced calcium influx [34]. The third site of 2-APB fixation is nested in a cavity formed by the extracellular portions of helices S1-S4 and is mediated through both hydrophobic and hydrophilic residues including V458, Y540, R487, and Q483 [22]. The binding of 2-APB on the first two sites described above does not induce gating-associated conformational changes. In opposite, dramatic structural rearrangements are observed when 2-APB binds the third site [22]. Thus, binding of 2-APB to the first two sites is likely a prerequisite for gating, by stabilizing the multiple domains during channel opening.

Endogenous ligands were also reported for TRPV1 and TRPV3: unsaturated N-acyldopamines, lipoxygenase products of arachidonic acid, linoleic acid, Phospholipase C metabolites, and the endocannabinoid anandamide [35].

2.5 Sensitization/desensitization

In both TRPV1 and TRPV3, the N-terminus module contains a domain able to bind calmodulin (CaM) in a Ca^{2+}-dependent manner [36]. This domain is located between the ankyrin repeats 2 and 3, which comprise a conserved site (K155 and K160 for TRPV1; K169 and K174 for TRPV3) involved in both CaM and ATP binding [37, 38]. In a resting cell, ATP is bound, and the channel is sensitized. Indeed, it has been shown that ATP binding to the TRPV1-ARD generates larger currents in response to capsaicin application [39, 40]. Hence, after channel opening, Ca^{2+} flows inward and chelates the ATP, which is released from TRPV1-ARD, thus freeing the binding site. In parallel, the Ca^{2+} influx activates CaM, and Ca^{2+}-CaM can replace the sensitizer and engages the ARD to close the channel [40]. Thus, CaM is involved in Ca^{2+}-dependent desensitization of TRPV1 [41].

The binding of ATP and Ca^{2+}-CaM to the N-terminal ARD observed in TRPV1 is conserved in TRPV3 [38], although differences exist. TRPV1 is desensitized after cumulative stimulations. In contrast, TRPV3 is the only member among the TRP channels that sensitizes upon repeated application of stimuli. In addition, the sensitization of TRPV3 is independent of the origin of the stimulus, it will sensitize regardless whether it is activated by heat or chemical ligands. TRPV3 also displays cross-sensitization to stimuli of a different nature, as camphor stimulation causes a

sensitization to heat [42]. It is known that sensitization is due to the decrease of the inhibition by calcium from both sides of cells [43]. In the intracellular side, Ca^{2+}-CaM binds ARD and inhibits TRPV3, as described above for TRPV1. The TRPV3-ARD structure is very close to ARD from other members of TRPV channel family, except it exhibits a unique particular conformation of finger 3 loop. This linker region in between the ankyrin repeats 3 and 4 is greatly stabilized by a network of hydrogen bonds and an hydrophobic environment, instead of being flexible as seen in the other TRPV-ARD arrangements [44]. This stabilized finger 3 of TRPV3-ARD may cause steric hindrance, which impedes the binding of CaM. Therefore, CaM binding to ARD probably forces a conformational change of finger 3, thus resulting in an inhibition of TRPV3 function. Upon successive simulations, the finger 3 of TRPV3-ARD undergoes conformational change that decreases the binding of CaM, causing the channel to open more easily. Thus, the finger 3 of TRPV3-ARD functions as a switch in regulation of TRPV3 upon stimulation. Moreover, this distinctive finger 3 segment precedes a conserved threonine 264, which has been identified as a putative site for the ERK1-dependent modulation of TRPV3 [45]. Phosphorylation events could, therefore, alter the conformation of this important loop and powerfully influence the binding of regulatory factors [46]. In others contexts, the influence of phosphorylation events has been demonstrated especially for TRPV1, where phosphorylation of the channel induces sensitization, whereas dephosphorylation is associated to desensitization [47]. The TRPV1 C-terminus also contains modulatory domains able to be phosphorylated and to bind CaM through the 35 amino acids segment E767–T801 [41, 48].

In contrast to TRPV1, the naive TRPV3 channel does not show any intrinsic voltage-dependent activation. The voltage dependence only appears when the TRPV3 channel is primo-stimulated by chemicals or heat stimulus [43, 49]. This voltage dependence of TRPV3 is established by Ca^{2+} binding on N641 at the pore loop after opening. In addition, the voltage dependence is strongly influenced by Ca^{2+}-CaM binding at the cytoplasmic N terminus. Sensitization is accompanied by a decrease in the voltage dependence. Finally, the sensitized TRPV3 channels are less inhibited than the naive ones, showing faster activation at positive potentials and less deactivation at negative potentials. This gradual shift in Ca^{2+}-dependent regulation or TRPV3 activity is likely related to conformational changes after successive stimulations [43, 44, 46]. Considering the huge complexity in the structural arrangement and interactions of the multiple domains of the TRPV channels, it has been difficult to fully decipher the mechanisms of gating, and many questions remain open.

3. TRPV1 and TRPV3 channels in skin function

3.1 Epidermal barrier function

Ca^{2+} is well known to contribute to epidermal homeostasis and thus to the formation of an effective skin barrier [50, 51]. In order to maintain its barrier function, the epidermis needs to be renewed every 28 days depending on a calcium gradient. The increase in calcium concentration in the outer layer is essential for the terminal differentiation of keratinocytes, which will lead to the formation of the *stratum corneum* and ensure the skin's physical barrier role [51]. This supports the role of calcium-permeable channels in epidermal barrier function.

The role of TRPV3 in the epidermal differentiation process was highlighted after aberrant expression of early differentiation markers (i.e., KRT1/KRT10) in keratinocytes from

Trpv3-KO mice [52]. In addition, the decrease in transglutaminase activity contributed to an alteration in the *stratum corneum* formation. This regulation of keratinocyte differentiation process appears to be dependent on the TRPV3/TGFα/EGFR signaling axis [52, 53]. These data support the importance of TRPV3 channels as actors in the balance between proliferation and differentiation, thus giving them a crucial role in skin barrier formation. In contrast, the contribution of TRPV1 channels in the skin barrier remains unknown.

3.2 Sensory modalities in the healthy skin

TRPV1 is a major nonselective cation channel with polymodal mechanisms of activation [54]. Functional TRPV1 serves as a thermal sensor since it is gated by noxious heat greater than 42°C and also chili pepper [9, 55]. The heat nociception was almost abolished following ablation of TRPV1-expressing neurons in mice [56], but *Trpv1*-knockout mice display only a partial defect in the ability to sense and respond to acute noxious heat [57]. Partial explanation could be that three channels, including TRPV1, TRPM3, and TRAP1, act in concert to mediate behavioral responses to noxious heat [58]. Besides heat, TRPV1 channels can be directly activated by proton, such as extracellular acidification (pH less than ~6.0) [9, 59]. Consistently, an integrative study performed in healthy rats has shown that cutaneous vasodilation in response to cathodal stimulation was induced by TRPV1 channels, likely through local acidification and the PGIS/PGI2/IP pathway [60].

In contrast to TRPV1, TRPV3 was reported as a warm sensor for innocuous temperatures (approximately 33°C) in different *in vitro* studies [13, 14, 16] . Not surprisingly, a profound deficit in sensing warm external temperatures was described in mice lacking Trpv3 [15]. Later it has been shown that *Trpv3*-KO mice displayed a preference toward cooler temperatures [61], showing that TRPV3 influences thermal information that is used to modulate thermal comfort or preference. TRPV3 on keratinocytes has been shown to play a role in thermosensation involving ATP signaling, but other molecules have also been reported [62] . The overexpression of TRPV3 in keratinocyte induces the release of PGE_2, an algogenic substance. Interestingly, in mice overexpressing Trpv3 channels selectively in keratinocytes, an hyperalgesia was observed [63]. These data support that TRPV3 channels participate to the thermal and pain transduction through these mediators. More recently, *in vivo* demonstration was provided for the role of cutaneous Trpv3 as a warm sensor of heating and a strong modulator of cutaneous vascular thermoregulatory mechanisms [64]. Since keratinocytes are representing the primary site of action of TRPV3 in mice (see the above section on TRPV3 expression), this study indicates that TRPV3 channels in the keratinocytes serve as heat detectors for warm temperatures to regulate cutaneous thermal homeostasis via initial changes in local blood flow. In contrast, TRPV1 channels are not involved in this process since *Trpv1*-KO mice displayed a normal heat-evoked vasodilation. It is interesting to note that *Trpv3*-KO mice showed a delay in behavioral response to noxious temperature over 50°C and 55°C, indicating that TRPV3 is also involved in response to acute painful heat stimuli [15]. This coincides with the ability to sensitize TRPV3 upon noxious heat stimuli [13]. Since *Trpv3*-KO mice and *Trpv1*-KO mice have an identical thermal nociceptive phenotype, this suggests that these two channels have overlapping thermal detection and functions.

4. TRPV1 and TRPV3 channels in psoriasis

Psoriasis is a chronic multifactorial inflammatory disease, resulting from the interaction between genetic predisposing factors and environmental triggers, with a

global incidence ranging between 0.09% and 5.1% [65]. This dermatosis results from altered signaling between epidermal keratinocytes and the immune system leading to an uncontrolled keratinocyte proliferation (hyperplasia), impaired keratinocyte differentiation (hyperkeratosis), and chronic inflammation. The immune cells (i.e., dendritic and T cells) infiltrating skin lesions produce a wide variety of cytokines (IL-23, IL-17, IFNγ), which activate keratinocytes [66, 67]. Once activated, keratinocytes produce pro-inflammatory cytokines (i.e., IL-6, TNFα), chemokines (i.e., CXCL1, CCL2, CCL13), and antimicrobial peptides (cathelicidin, β-defensine) that further stimulate immune cells and thus maintain the disease in a chronic state. Therefore, keratinocytes not only respond to inflammation but also contribute to the recruitment and the activation of immune cells. Moreover, TRPV1 and TRPV3 channels have a predominant role in inflammation, pain, and pruritus and could be involved in the vicious cycle of the inflammation process in psoriasis.

Indeed, TRPV1 overexpression has been found in the skin of psoriatic patients and in the mouse model of "imiquimod-induced psoriasis" [68, 69]. Imiquimod (IMQ) is a potent immune activator stimulating the IL-23/IL-17 axis and thus mimicking psoriasis inflammation [70]. In 2014, Riol-Blanco *et al* have shown that ablation by RTX of TRPV1$^+$/NaV1.8$^+$ nociceptors reduces immune cells infiltration and psoriasis skin inflammation, by acting on IL-23 and IL17 release (**Figure 3**) [71]. Furthermore, this study revealed that TRPV1$^+$/NaV1.8$^+$ nociceptors can interact with dermal dendritic cells to regulate the IL-23/IL-17 axis during the initiation phase of psoriasis. Further data support a role for TRPV1 in this skin disease. In 2018, Zhou *et al.* also highlighted a significant decrease in epidermal hyperplasia, inflammatory cell infiltration, and cytokine production (IL-1, IL-6, IL-23) in IMQ-treated *Trpv1*-KO mice [69]. The NGF-TrkA-TRPV1 signaling pathway in nerve fibers has also been shown to play a role in psoriasis lesion formation [72]. Indeed, both nerve growth factor (NGF) and Tropomyosin receptor kinase A (TrkA) are highly expressed in psoriasis, and their interaction induces activation of TRPV1-mediated pain and pruritus [72–74]. Consistently, a TrkA kinase inhibitor (CT327) reduced pruritus of psoriatic patients (15). It is possible that NGF could sensitize TRPV1 channels on nerve fibers (NaV1.8$^+$) during the initiation phase and then stimulate innate immune dermal dendric cells for the induction of IL-23/IL-17 signaling, leading to the development of psoriasis. Together, these data confirm the involvement of TRPV1 in psoriasis, with a major role of sensory nerve fibers.

In contrast to TRPV1, TRPV3 channels seem to act on psoriasis from upper cell layers, such as keratinocytes. Indeed, TRPV3 channel expression is increased in psoriatic skin lesions, with significant labeling within the epidermis [68, 75]. Moreover, many studies have supported the role of TRPV3 on inflammation. Upon stimulation, TRPV3 can activate the EGFR/NFκB pathway and induce the release of mediators, such as IL-1α, IL-6, IL-8, TNFα, ATP, and PGE2 [53, 76], which will in turn act on sensory nerves and provoke pain and itching [62, 63]. In addition, Zhao *et al.* recently proposed that protease-activated receptor (PAR2) sensitizes TRPV3 channels on keratinocytes, resulting in secretion of thymic stromal lymphopoietin (TSLP), a potent pro-inflammatory cytokine. The latter then contributes to the production of IL-23 by dendritic cells and induces severe itching [77, 78]. Finally, the TRPV3 gain-of-function mutations G573S or G573C result in hyperkeratosis in mice, increased inflammatory cytokines in serum (IL-1α, Il-6, IL-17), and high levels of pruritogenic substances, such as NGF (**Figure 3**) [79, 80]. To further endorse the role of TRPV3 in inflammation, the 17(R)-resolvin D1, an anti-inflammatory lipid, is able to suppress TRPV3-induced hypersensitivity/pain during the inflammatory response
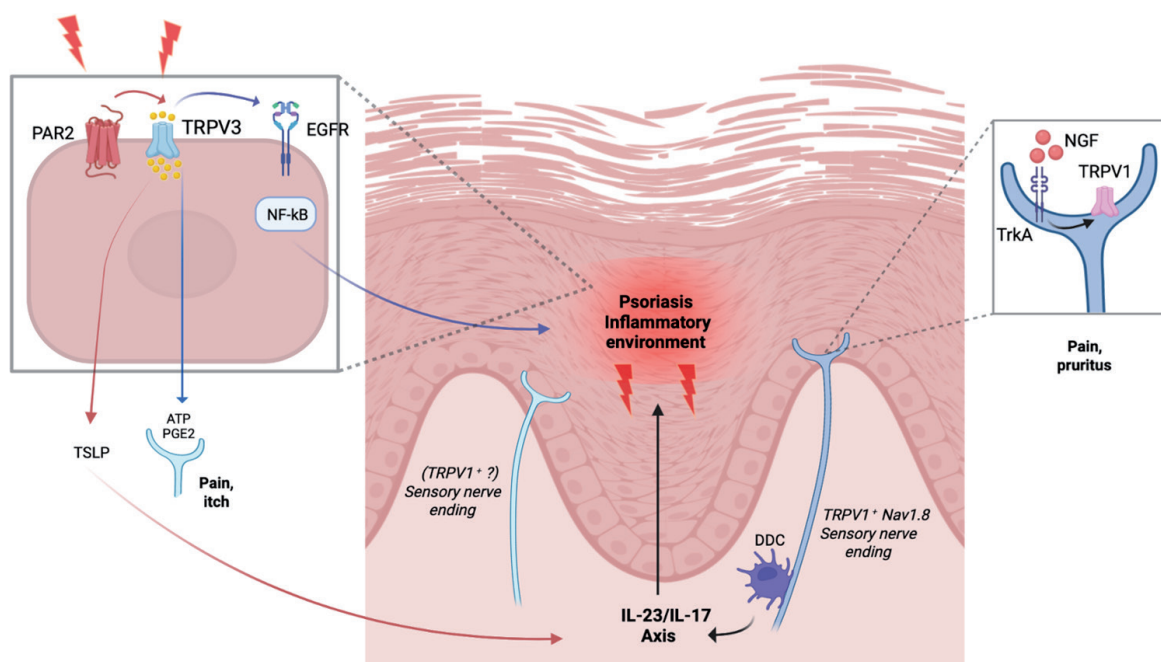
Figure 3.
TRPV1 and TRPV3 in the physiopathology of psoriasis. Left – Inflammatory environment in skin psoriasis stimulates PAR2 on keratinocytes. Activated PAR2 stimulates TRPV3, which leads to the production of TSLP, an activator of the IL-23/IL-17 axis (red arrows). Inflammation also directly activates TRPV3, which leads to the production and the fixation of ATP and PGE2 on C-fibers, leading to pain and itch (blue arrows). Activated TRPV3 also stimulates and activates EGFR. In this context, the EGFR activation induces the transcription of NF-κB, allowing the production of inflammatory cytokines that sustain the inflammatory process in the skin. Right – In a psoriasis skin, keratinocytes release NGF in the extracellular environment. NGF can interact with TrkA present on the TRPV1+/Nav1.8 nerve endings. This interaction activates TRPV1 and leads to pain and pruritus. The interaction of dermal dendritic cells (DDC) with TRPV1+/Nav1.8 nerve endings potentiates the activation of the IL-23/IL-17 axis.

in mice [81]. Moreover, injection of the TRPV3 antagonist 74a is able to attenuate pruritus and inflammatory response in mice with chronic inflammatory disease such as atopic dermatitis [77]. Thus, either through the activation of signaling pathways (EGFR/NFκB; PAR2) or the release of algogenic and pruritogenic mediators, TRPV3 channels appear to play a role in the initiation of psoriasis.

Altogether, these data support that TRPV1 and TRPV3 are actors of inflammation, either from sensory nerve fibers or from keratinocytes. Both channels seem to have fundamental role in the pathogenesis of psoriasis due to their ability to activate immune cells or to induce cytokine production. It could also be hypothesized that these two channels cooperate during the initiation process of psoriasis.

5. TRPV1 and TRPV3 channels in therapeutic perspectives of psoriasis

The well-known biological strategies to treat an inflammatory disease such as psoriasis consist of using a specific blocking antibody to freeze the interaction of a cytokine with its receptor and then blocking the underlying cytokine-specific biological response. As mentioned earlier, both TRPV1 and TRPV3 are involved in the inflammatory process of psoriasis and could also be potential therapeutic targets in this disease. Indeed, TrkA appears to be a potential target because its inhibition with CT327 blocks the overactivation of TRPV1 on sensory neurons. The discovery of this new molecule is promising since the decrease in pain and pruritus has been observed

in psoriatic patients [72]. Interestingly, another study also demonstrated a decrease in skin hyperplasia and erythema in psoriasis murine models treated with the TRPV1 antagonist SB366791 [82]. Research on the inhibition of TRPV1 in psoriasis disease has already emerged and needs to be further explored.

As the TRPV3/TGFα/EGFR signaling complex seems to play a role in psoriasis, EGFR also becomes a potential therapeutic target. A recent clinical study showed that erlotinib, an EGFR inhibitor, significantly decreases hyperkeratosis and pain in Olmsted syndrome patients displaying a TRPV3 overactivation mutation [83]. This highlights that inhibition of EGFR could decrease keratinocytes hyperproliferation/differentiation and might also act on inflammation and pain. Since TRPV3 acts at the first line, directly targeting this channel could also be very promising. Indeed, we reported above some anti-inflammatory molecules, such as 17(R)-resolvin D1, which suppresses TRPV3-induced pain and inflammation. Another potential promising molecule is the TRPV3 antagonist called 74a, which has already proved its efficacy on another inflammatory skin disease [77].

It could be suggested that inflammatory environment activates TRPV3 from keratinocytes and TRPV1+ nerves for the induction of pain, itching, and inflammation. The cooperation of these two channels, with the potential activation of TRPV1 induced by downstream mediators of TRPV3, cannot be excluded. To increase further the complexity of the TRPV1 and TRPV3 relationship, it has been demonstrated that TRPV1 and TRPV3 could form interacting partners, therefore assembling heterochannels [84, 85]. The biological significance of these heterochannels is still not known, but this could be involved in a very fine-tuning of sensitivity. In addtion, a recent study showed that the intergenic region between TRPV1 and TRPV3 coding sequences contained a human specific transposable element (SVA: SINE-VNTR-Alu retrotransposon) insertion, located upstream of the TRPV3 promoter and downstream of the 3′ end of TRPV1 [86]. This SVA insertion acts as a cis-regulatory element allowing coexpression of TRPV1 and TRPV3 in multiple human tissues, which is not observed in mice. Thus, targeting these two channels simultaneously could be a very promising approach for the treatment of psoriasis in human.

6. Conclusion

TRPV1 and TRPV3 are important channels for maintaining the skin homeostasis and its function. A deregulation of their expression and/or activity is associated to the establishment of an inflammatory response. Several studies already demonstrated their contribution in psoriasis by highlighting their capacities to activate typical inflammatory pathways (IL-23/IL-17 axis, NF-κB pathway) and/or to provoke the release of inflammatory mediators. It would therefore be interesting to explore the exact contribution of TRPV1 and TRPV3 in the psoriasis typical chronic skin inflammation: are they the trigger or are they one of the multiple factors involved in maintaining inflammation?

It would be interesting to explore the presence of TRPV1 and TRPV3 in other tissues of the body subjected to chronic inflammation, such as the intestinal epithelium. The future challenge will be to develop specific compounds that target the TRPV1/TRPV3 to limit chronic inflammation without affecting their physiological functions.

Conflict of interest

The authors declare no conflict of interest.

Notes

All of the artworks used were adapted from the illustration bank of Biorender (https://biorender.com).

Author details

Lisa S. Martin[1,2], Emma Fraillon[1,2], Fabien P. Chevalier[1,2]* and Bérengère Fromy[1,2]*

1 CNRS UMR 5305, Tissue Biology and Therapeutic Engineering Laboratory, Lyon, France

2 Claude Bernard University Lyon 1, Villeurbanne, France

*Address all correspondence to: fabien.chevalier@univ-lyon1.fr
and berengere.fromy@univ-lyon1.fr

IntechOpen

References

[1] Wong R, Geyer S, Weninger W, Guimberteau J-C, Wong JK. The dynamic anatomy and patterning of skin. Experimental Dermatology. 2016;**25**(2):92-98

[2] Khavkin J, Ellis DAF. Aging Skin: Histology, Physiology, and Pathology. Facial Plastic Surgery Clinics of North America. 2011;**19**(2):229-234

[3] Roosterman D, Goerge T, Schneider SW, Bunnett NW, Steinhoff M. Neuronal Control of Skin Function: The Skin as a Neuroimmunoendocrine Organ. Physiological Reviews. 2006;**86**(4):1309-1379

[4] Talagas M, Lebonvallet N, Leschiera R, Marcorelles P, Misery L. What about physical contacts between epidermal keratinocytes and sensory neurons? Experimental Dermatology. 2018;**27**(1):9-13

[5] Denda M, Nakatani M, Ikeyama K, Tsutsumi M, Denda S. Epidermal keratinocytes as the forefront of the sensory system. Experimental Dermatology. 2007;**16**(3):157-161

[6] Moehring F, Cowie AM, Menzel AD, Weyer AD, Grzybowski M, Arzua T, et al. Keratinocytes mediate innocuous and noxious touch via ATP-P2X4 signaling. eLife. 2018;**7**:e31684

[7] Venkatachalam K, Montell C. TRP Channels. Annual Review of Biochemistry. 2007;**76**:387-417

[8] Voets T. TRP channels and thermosensation. Handbook of Experimental Pharmacology. 2014;**223**:729-741

[9] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;**389**(6653):816-824

[10] Bodó E, Kovács I, Telek A, Varga A, Paus R, Kovács L, et al. Vanilloid Receptor-1 (VR1) is Widely Expressed on Various Epithelial and Mesenchymal Cell Types of Human Skin. The Journal of Investigative Dermatology. 2004;**123**(2):410-413

[11] Ständer S, Moormann C, Schumacher M, Buddenkotte J, Artuc M, Shpacovitch V, et al. Expression of vanilloid receptor subtype 1 in cutaneous sensory nerve fibers, mast cells, and epithelial cells of appendage structures. Experimental Dermatology. 2004;**13**(3):129-139

[12] Denda M, Fuziwara S, Inoue K, Denda S, Akamatsu H, Tomitaka A, et al. Immunoreactivity of VR1 on epidermal keratinocyte of human skin. Biochemical and Biophysical Research Communications. 2001;**285**(5):1250-1252

[13] Peier AM. A Heat-Sensitive TRP Channel Expressed in Keratinocytes. Science. 2002;**296**(5575):2046-2049

[14] Xu H, Ramsey IS, Kotecha SA, Moran MM, Chong JA, Lawson D, et al. TRPV3 is a calcium-permeable temperature-sensitive cation channel. Nature. 2002;**418**(6894):181-186

[15] Moqrich A. Impaired Thermosensation in Mice Lacking TRPV3, a Heat and Camphor Sensor in the Skin. Science. 2005;**307**(5714):1468-1472

[16] Smith GD, Gunthorpe MJ, Kelsell RE, Hayes PD, Reilly P, Facer P, et al. TRPV3 is a temperature-sensitive

vanilloid receptor-like protein. Nature. 2002;**418**(6894):186-190

[17] Voets T, Droogmans G, Wissenbach U, Janssens A, Flockerzi V, Nilius B. The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels. Nature. 2004;**430**(7001):748-754

[18] Nilius B, Talavera K, Owsianik G, Prenen J, Droogmans G, Voets T. Gating of TRP channels: a voltage connection? The Journal of Physiology. 2005;**567** (Pt 1):35-44

[19] Cao E. Structural mechanisms of transient receptor potential ion channels. Journal of General Physiology. 2020;**152**(3):e201811998

[20] Liao M, Cao E, Julius D, Cheng Y. Structure of the TRPV1 ion channel determined by electron cryo-microscopy. Nature. 2013;**504**(7478):107-112

[21] García-Sanz N, Fernández-Carvajal A, Morenilla-Palao C, Planells-Cases R, Fajardo-Sánchez E, Fernández-Ballester G, et al. Identification of a tetramerization domain in the C terminus of the vanilloid receptor. The Journal of Neuroscience. 2004;**24**(23):5307-5314

[22] Singh AK, McGoldrick LL, Sobolevsky AI. Structure and gating mechanism of the transient receptor potential channel TRPV3. Nature Structural & Molecular Biology. 2018;**25**(9):805-813

[23] Chung M-K, Güler AD, Caterina MJ. TRPV1 shows dynamic ionic selectivity during agonist stimulation. Nature Neuroscience. 2008;**11**(5):555-564

[24] Cui Y, Yang F, Cao X, Yarov-Yarovoy V, Wang K, Zheng J. Selective disruption of high sensitivity

heat activation but not capsaicin activation of TRPV1 channels by pore turret mutations. Journal of General Physiology. 2012;**139**(4):273-283

[25] Yang F, Cui Y, Wang K, Zheng J. Thermosensitive TRP channel pore turret is part of the temperature activation pathway. Proceedings of the National Academy of Sciences. 2010;**107**(15):7083-7088

[26] Grandl J, Hu H, Bandell M, Bursulaya B, Schmidt M, Petrus M, et al. Pore region of TRPV3 ion channel is specifically required for heat activation. Nature Neuroscience. 2008;**11**(9):1007-1013

[27] Colton CK, Zhu MX. 2-Aminoethoxydiphenyl Borate as a Common Activator of TRPV1, TRPV2, and TRPV3 Channels. In: Flockerzi V, Nilius B, éditeurs. Transient Receptor Potential (TRP) Channels. Berlin, Heidelberg: Springer Berlin Heidelberg; 2007. p. 173-187. (Handbook of Experimental Pharmacology; vol. 179).

[28] Siemens J, Zhou S, Piskorowski R, Nikai T, Lumpkin EA, Basbaum AI, et al. Spider toxins activate the capsaicin receptor to produce inflammatory pain. Nature. 2006;**444**(7116):208-212

[29] Vriens J, Appendino G, Nilius B. Pharmacology of vanilloid transient receptor potential cation channels. Molecular Pharmacology. 2009;**75**(6):1262-1279

[30] Jordt S-E, Julius D. Molecular basis for species-specific sensitivity to hot chili peppers. Cell. 2002;**108**(3):421-430

[31] Marín-Burgin A, Reppenhagen S, Klusch A, Wendland JR, Petersen M. Low-threshold heat response antagonized by capsazepine in chick sensory neurons, which are capsaicin-insensitive. The

European Journal of Neuroscience. 2000;**12**(10):3560-3566

[32] Broad LM, Mogg AJ, Eberle E, Tolley M, Li DL, Knopp KL. TRPV3 in Drug Development. Pharmaceuticals (Basel). 2016;**9**(3):55

[33] Hu H, Grandl J, Bandell M, Petrus M, Patapoutian A. Two amino acid residues determine 2-APB sensitivity of the ion channels TRPV3 and TRPV4. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(5):1626-1631

[34] Deering-Rice CE, Mitchell VK, Romero EG, Abdel Aziz MH, Ryskamp DA, Križaj D, et al. Drofenine: a 2-APB analog with improved selectivity for human TRPV3. Pharmacology Research & Perspectives. 2014;**2**(5)

[35] Van Der Stelt M, Di Marzo V, Endovanilloids. Putative endogenous ligands of transient receptor potential vanilloid 1 channels. European Journal of Biochemistry. 2004;**271**(10):1827-1834

[36] Rosenbaum T, Gordon-Shaag A, Munari M, Gordon SE. Ca2+/calmodulin modulates TRPV1 activation by capsaicin. The Journal of General Physiology. 2004;**123**(1):53-62

[37] Nilius B, Bíró T, Owsianik G. TRPV3: time to decipher a poorly understood family member!: TRPV3. The Journal of Physiology. 2014;**592**(2):295-304

[38] Phelps CB, Wang RR, Choo SS, Gaudet R. Differential Regulation of TRPV1, TRPV3, and TRPV4 Sensitivity through a Conserved Binding Site on the Ankyrin Repeat Domain. Journal of Biological Chemistry. 2010;**285**(1):731-740

[39] Lau S-Y, Procko E, Gaudet R. Distinct properties of Ca2+−calmodulin binding to N- and C-terminal regulatory regions of the TRPV1 channel. Journal of General Physiology. 2012;**140**(5):541-555

[40] Lishko PV, Procko E, Jin X, Phelps CB, Gaudet R. The Ankyrin Repeats of TRPV1 Bind Multiple Ligands and Modulate Channel Sensitivity. Neuron. 2007;**54**(6):905-918

[41] Numazaki M, Tominaga T, Takeuchi K, Murayama N, Toyooka H, Tominaga M. Structural determinant of TRPV1 desensitization interacts with calmodulin. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(13):8002-8006

[42] Moqrich A, Hwang SW, Earley TJ, Petrus MJ, Murray AN, Spencer KSR, et al. Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. Science. 2005;**307**(5714):1468-1472

[43] Xiao R, Tang J, Wang C, Colton CK, Tian J, Zhu MX. Calcium Plays a Central Role in the Sensitization of TRPV3 Channel to Repetitive Stimulations. Journal of Biological Chemistry. 2008;**283**(10):6162-6174

[44] Shi D-J, Ye S, Cao X, Zhang R, Wang K. Crystal structure of the N-terminal ankyrin repeat domain of TRPV3 reveals unique conformation of finger 3 loop critical for channel function. Protein & Cell. 2013;**4**(12):942-950

[45] Vyklicka L, Boukalova S, Macikova L, Chvojka S, Vlachova V. The human transient receptor potential vanilloid 3 channel is sensitized via the ERK pathway. Journal of Biological Chemistry. 2017;**292**(51):21083-21091

[46] Latorre R, Brauchi S, Orta G, Zaelzer C, Vargas G. ThermoTRP channels as modular proteins with

allosteric gating. Cell Calcium. 2007;**42**(4-5):427-438

[47] Yao X, Kwan H-Y, Huang Y. Regulation of TRP Channels by Phosphorylation. Neuro-Signals. 2005;**14**(6):273-280

[48] Huang J, Zhang X, McNaughton PA. Modulation of temperature-sensitive TRP channels. Seminars in Cell & Developmental Biology. 2006;**17**(6):638-645

[49] Liu B, Yao J, Zhu MX, Qin F. Hysteresis of gating underlines sensitization of TRPV3 channels. Journal of General Physiology. 2011;**138**(5):509-520

[50] Lee SE, Lee SH. Skin Barrier and Calcium. Annals of Dermatology. 2018;**30**(3):265-275

[51] Baroni A, Buommino E, De Gregorio V, Ruocco E, Ruocco V, Wolf R. Structure and function of the epidermis related to barrier properties. Clinics in Dermatology. 2012;**30**(3):257-262

[52] Cheng X, Jin J, Hu L, Shen D, Dong X, Samie MA, et al. TRP Channel regulates EGFR signaling in Hair Morphogenesis and Skin Barrier Formation. Cell. 2010;**141**(2): 331-343

[53] Wang Y, Li H, Xue C, Chen H, Xue Y, Zhao F, et al. TRPV3 enhances skin keratinocyte proliferation through EGFR-dependent signaling pathways. Cell Biology and Toxicology. 2020;**37**(2):313-330. DOI: 10.1007/s10565-020-09536-2

[54] Bourinet E, Altier C, Hildebrand ME, Trang T, Salter MW, Zamponi GW. Calcium-permeable ion channels in pain signaling. Physiological Reviews. 2014;**94**(1):81-140

[55] Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. Annual Review of Neuroscience. 2001;**24**:487-517

[56] Binshtok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. Nature. 2007;**449**(7162):607-610

[57] Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science. 2000;**288**(5464):306-313

[58] Vandewauw I, De Clercq K, Mulier M, Held K, Pinto S, Van Ranst N, et al. A TRP channel trio mediates acute noxious heat sensing. Nature. 2018;**555**(7698):662-666

[59] Jordt SE, Tominaga M, Julius D. Acid potentiation of the capsaicin receptor determined by a key extracellular site. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**(14):8134-8139

[60] Gohin S, Decorps J, Sigaudo-Roussel D, Fromy B. Sensory nerves contribute to cutaneous vasodilator response to cathodal stimulation in healthy rats. Microvascular Research. 2015;**101**:103-110

[61] Marics I, Malapert P, Reynders A, Gaillard S, Moqrich A. Acute Heat-Evoked Temperature Sensation Is Impaired but Not Abolished in Mice Lacking TRPV1 and TRPV3 Channels. PLoS One. 2014;**9**(6):e99828

[62] Mandadi S, Sokabe T, Shibasaki K, Katanosaka K, Mizuno A, Moqrich A, et al. TRPV3 in keratinocytes transmits temperature information to sensory neurons via ATP. Pflügers Archiv. 2009;**458**(6):1093-1102

[63] Huang SM, Lee H, Chung M-K, Park U, Yu YY, Bradshaw HB, et al. Overexpressed Transient Receptor Potential Vanilloid 3 Ion Channels in Skin Keratinocytes Modulate Pain Sensitivity via Prostaglandin E2. The Journal of Neuroscience. 2008;**28**(51):13727-13737

[64] Fromy B, Josset-Lamaugarny A, Aimond G, Pagnon-Minot A, Marics I, Tattersall GJ, et al. Disruption of TRPV3 Impairs Heat-Evoked Vasodilation and Thermoregulation: A Critical Role of CGRP. Journal of Investigative Dermatology. 2018;**138**(3):688-696

[65] Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. Journal of the European Academy of Dermatology and Venereology. 2017;**31**(2):205-212

[66] Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of Psoriasis. Annual Review of Immunology. 2014;**32**:227-255

[67] Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. International Journal of Molecular Sciences. 2019;**20**(6):1475

[68] Nattkemper LA, Tey HL, Valdes-Rodriguez R, Lee H, Mollanazar NK, Albornoz C, et al. The Genetics of Chronic Itch: Gene Expression in the Skin of Patients with Atopic Dermatitis and Psoriasis with Severe Itch. The Journal of Investigative Dermatology. 2018;**138**(6):1311-1317

[69] Zhou Y, Follansbee T, Wu X, Han D, Yu S, Domocos DT, et al. TRPV1 mediates inflammation and hyperplasia in imiquimod (IMQ)-induced psoriasiform dermatitis (PsD) in mice. Journal of Dermatological Science. 2018;**92**(3):264-271

[70] Fits L v d, Mourits S, JSA V, Kant M, Boon L, Laman JD, et al.

Imiquimod-Induced Psoriasis-Like Skin Inflammation in Mice Is Mediated via the IL-23/IL-17 Axis. The Journal of Immunology. 2009;**182**(9):5836-5845

[71] Nociceptive Sensory Neurons Drive Interleukin-23 Mediated Psoriasiform Skin Inflammation. Nature. 2022;**510**(7503):157-161

[72] Roblin D, Yosipovitch G, Boyce B, Robinson J, Sandy J, Mainero V, et al. Topical TrkA Kinase Inhibitor CT327 is an Effective, Novel Therapy for the Treatment of Pruritus due to Psoriasis: Results from Experimental Studies, and Efficacy and Safety of CT327 in a Phase 2b Clinical Trial in Patients with Psoriasis. Acta Dermato-Venereologica. 2015;**95**(5):542-548

[73] Zhang X, Huang J, McNaughton PA. NGF rapidly increases membrane expression of TRPV1 heat-gated ion channels. The EMBO Journal. 2005;**24**(24):4211-4223

[74] Raychaudhuri SP, Raychaudhuri SK. Role of NGF and neurogenic inflammation in the pathogenesis of psoriasis. Progress in Brain Research. 2004;**146**:433-437

[75] Seo S, Kim S, Kim S-E, Chung S, Lee S. Enhanced Thermal Sensitivity of TRPV3 in Keratinocytes Underlies Heat-Induced Pruritogen Release and Pruritus in Atopic Dermatitis. Journal of Investigative Dermatology. 2020;**140**(11):2199-2209.e6

[76] Szöllősi AG, Vasas N, Angyal Á, Kistamás K, Nánási PP, Mihály J, et al. Activation of TRPV3 Regulates Inflammatory Actions of Human Epidermal Keratinocytes. Journal of Investigative Dermatology. 2018;**138**(2):365-374

[77] Zhao J, Munanairi A, Liu X-Y, Zhang J, Hu L, Hu M, et al. PAR2

Mediates Itch via TRPV3 Signaling in Keratinocytes. The Journal of Investigative Dermatology. 2020;**140**(8):1524-1532

[78] El-Ghareeb MI, Helmy A, Al Kazzaz S, Samir H. Serum TSLP is a potential biomarker of psoriasis vulgaris activity. Psoriasis (Auckl). 2019;**9**:59-63

[79] Yoshioka T, Imura K, Asakawa M, Suzuki M, Oshima I, Hirasawa T, et al. Impact of the Gly573Ser Substitution in TRPV3 on the Development of Allergic and Pruritic Dermatitis in Mice. Journal of Investigative Dermatology. 2009;**129**(3):714-722

[80] Imura K, Yoshioka T, Hirasawa T, Sakata T. Role of TRPV3 in immune response to development of dermatitis. Journal of Inflammation (Lond). 2009;**6**:17

[81] Bang S, Yoo S, Yang T, Cho H, Hwang S. 17(R)-resolvin D1 specifically inhibits transient receptor potential ion channel vanilloid 3 leading to peripheral antinociception. British Journal of Pharmacology. 2012;**165**(3):683-692

[82] Kemény Á, Kodji X, Horváth S, Komlódi R, Szőke É, Sándor Z, et al. TRPA1 Acts in a Protective Manner in Imiquimod-Induced Psoriasiform Dermatitis in Mice. The Journal of Investigative Dermatology. 2018;**138**(8):1774-1784

[83] Greco C, Leclerc-Mercier S, Chaumon S, Doz F, Hadj-Rabia S, Molina T, et al. Use of Epidermal Growth Factor Receptor Inhibitor Erlotinib to Treat Palmoplantar Keratoderma in Patients With Olmsted Syndrome Caused by TRPV3 Mutations. JAMA Dermatology. 2020;**156**(2):191-195

[84] Smith GD, Gunthorpe MJ, Kelsell RE, Hayes PD, Reilly P, Facer P,

et al. TRPV3 is a temperature-sensitive vanilloid receptor-like protein. Nature. 2002;**418**(6894):186-190

[85] Cheng W, Yang F, Liu S, Colton CK, Wang C, Cui Y, et al. Heteromeric heat-sensitive transient receptor potential channels exhibit distinct temperature and chemical response. The Journal of Biological Chemistry. 2012;**287**(10):7279-7288

[86] Price E, Gianfrancesco O, Harrison PT, Frank B, Bubb VJ, Quinn JP. CRISPR Deletion of a SVA Retrotransposon Demonstrates Function as a cis-Regulatory Element at the TRPV1/TRPV3 Intergenic Region. IJMS. 2021;22(4):1911.