MINIREVIEW—MOLECULAR PHARMACOLOGY IN CHINA

The Ca^{2+} -Permeable Cation Transient Receptor Potential TRPV3 Channel: An Emerging Pivotal Target for Itch and Skin Diseases

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ABSTRACT

Temperature-sensitive transient receptor potential (TRP) channels such as TRPA1 and TRPV1 have been identified as downstream ion channel targets in the transduction of itch. As a member of the temperature-sensitive TRP family, the Ca^{2+} -permeable nonselective cation channel TRPV3 is expressed abundantly in skin keratinocytes. Recent identification of gain-of-function mutations of human TRPV3 from patients with Olmsted

syndrome, which is characterized by severe itching and palmoplantar and periorificial keratoderma, unveils its crucial role in chronic itch and skin diseases. In this review, we will focus on recent progress made in the understanding of TRPV3 that emerges as an attractive target for developing effective antipruritic therapy for chronic itch or skin-related diseases.

Introduction

Itch (also known as pruritus) is an unpleasant sensation of the skin, provoking the desire or reflex to scratch. Although acute itch is often caused in the local affected skin by pruritogens (e.g., histamine, allergens, inflammatory mediators, and drugs), chronic itch that impairs quality of life can be an indicator of widespread symptoms associated with cancers and inflammatory skin, infectious, immune, and liver diseases. With the exception of histamine-induced itch, there is generally no accepted treatment of chronic itch, which is still an unmet medical need. The lack of effective itch therapies is primarily attributed to the insufficient understanding of the crucial target(s) that underlies the pathogenesis of itch. Previous findings have shown that several subtypes of transient receptor potential (TRP) channels play important roles in different types of itch induced by pruritogens in rodents (see Zhang, 2015). However, the recent identification of gain-of-function mutations in human TRPV3 from patients with Olmsted syndrome characterized by severe itching and skin diseases unveils the crucial role of TRPV3 channels in itch signaling (Fig. 1). As a result, TRPV3 emerges as an

attractive target for developing antipruritic therapy in chronic itch or skin-related diseases.

The superfamily of TRP channels is composed of 28 mammalian or 27 human members that can be subdivided in six subfamilies, including the TRP subfamily A (ankyrin, TRPA), the TRP subfamily C (canonical, TRPC), the TRP subfamily M (melastatin, TRPM), the TRP polycystin subfamily (TRPP), the TRP mucolipin subfamily (TRPML), and the TRP subfamily V (vanilloid, TRPV) (Holzer and Izzo, 2014). Most TRP channels as homo- or probably heterotetramers permeate cations through central nonselective cation entry pores that are symmetrically located in the plasma membrane (Moiseenkova-Bell and Wensel, 2009). In general, TRP channels open and close in response to changes in temperature, chemical stimulation, ligand binding, and weak membrane depolarization (Nilius et al., 2005; Klein et al., 2015; Laing and Dhaka, 2016).

The Properties of TRPV3 Channels

Among the temperature-sensitive or thermoTRPV1–4 channels, TRPV3 exhibits distinct temperature activation at $>33^\circ\text{C}$ compared with TRPV1, TRPV2, and TRPV4, which are activated at $>43^\circ\text{C}$, $>52^\circ\text{C}$, and $>30^\circ\text{C}$, respectively (Ferrer-Montiel et al., 2012). As a thermosensor, TRPV3 appears as a surprise, in that it is poorly detected in the dorsal root

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ABBREVIATIONS: 2-APB, 2-aminoethoxydiphenyl borate; 17R-RvD1, 17(R)-resolvin D1; AD, atopic dermatitis; AEW, acetone/ether/water; ARD, ankyrin repeat domain; CaM, calmodulin; DRG, dorsal root ganglion; EGFR, epidermal growth factor receptor; HEK293, human embryonic kidney 293; PGE₂, prostaglandin E₂; PIP₂, phosphatidylinositol 4,5-bisphosphate; TG, transglutaminase; TGF- α , transforming growth factor- α ; TRP, transient receptor potential; W-7, N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide hydrochloride.

Fig. 1. Proposed role of TRPV3 in itch signaling and hair growth. TRPV3 is abundantly expressed in keratinocytes, the predominant cell type comprising the layers of the epidermis in the skin. Keratinocytes release numerous inflammatory molecules such as histamine, TSLP, chemokines, and cytokines, accounting for enhanced pruriceptor sensitivity under chronic itch conditions. The TRPV3 channel is activated by mechanisms that include elevated intracellular acidification (protons), temperature, activators, and other unidentified cellular events, resulting in an elevation of Ca^{2+} -dependent production and release of TGF- α or other EGFR ligands. TGF- α in turn stimulates EGFR, which physically associates with TRPV3 to form a signaling complex, and consequently sensitizes the responses of TRPV3 to endogenous activation. Thus, a positive feedback loop is formed between TRPV3 and TGF- α /EGFR, likely resulting in terminal differentiation of suprabasal keratinocytes that are actively participated in reepithelialization, wound closure, and hair morphogenesis. Coexpression of TRPV3 with TRPV1 enhances the capsaicin- or proton-evoked rise of intracellular Ca^{2+} concentrations, suggesting a physical association between the two proteins. Binding of ATP to conserved sites in the N-terminal ARD domains shared by TRPV3 and TRPV1 channels also suggests functional interactions between the two channels. ADAM17, metalloprotease ADAM17; ERK, extracellular signal-regulated kinase; CNS, central nervous system; DAG, diacylglycerol; IP_3 , inositol trisphosphate; PLC, phospholipase C; TSLP, thymic stromal lymphopoietin.

ganglion (DRG) or the trigeminal ganglion (TG) sensory neurons in rodents. Reports suggest that keratinocytes may release diffusible molecules that in turn can activate free nerve endings of neighboring DRG neurons when TRPV3 is activated by temperatures of $>32^\circ\text{C}$ in the skin (Mandadi et al., 2009; Gifford et al., 2012). This hypothesis was tested by coculturing TRPV3-deficient DRG neurons with keratinocytes (Mandadi et al., 2009). It was shown that the cytosolic concentration of Ca^{2+} in DRG sensory neurons was increased upon heating only when they were cocultured with keratinocytes, and the increase of intracellular calcium can be inhibited by suramin, P2 purinergic antagonists, and pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid tetrasodium salt (Mandadi et al., 2009). In cocultured keratinocytes and human embryonic kidney 293 (HEK293) cells, keratinocytes release ATP upon heating; this response is reduced in TRPV3-knockout mouse keratinocytes (Mandadi et al., 2009), suggesting that ATP can function as a messenger molecule for thermotransduction mediated by TRPV3 in the skin. Keratinocytes release ATP, and ATP accumulation in the interstitial fluid has been detected using microdialysis (Mandadi et al., 2009; Gifford et al., 2012).

TRPV3 belongs to the TRPV channel subfamily comprising six members. In humans, the gene for TRPV3, which contains 18 exons, is located on chromosome 17p13 in close proximity to the TRPV1 gene. Similar to human TRPV3, the mouse TRPV3 gene also has 18 exons and is located in chromosome 11B4 (Peier et al., 2002; Smith et al., 2002; Xu et al., 2002). The

complete open reading frame of the mouse or human TRPV3 gene is 2373 bp, encoding for a polypeptide containing 791 amino acids. However, the TRPV3 gene may be differentially spliced, yielding 790, 791, and 765 amino acid variants in humans (Smith et al., 2002; Xu et al., 2002). It has been shown by in situ hybridization and reverse transcription polymerase chain reaction analysis that TRPV3 is most abundantly expressed in keratinocytes of the skin as well as in oral and nasal epithelia in both humans and mice (Moqrich et al., 2005; Xu et al., 2006; Ahmed et al., 2009). TRPV3 is also detected in the brain, spinal cord, DRG, TG, and testes in humans (Peier et al., 2002; Smith et al., 2002; Xu et al., 2002) but is not highly expressed in the DRG or TG in rodents (Peier et al., 2002; Moqrich et al., 2005).

There is an ankyrin repeat domain (ARD) in the intracellular N terminus in all six members of the TRPV subfamily. Each ankyrin repeat is typically composed of 33 residues that function as a motif that is primarily involved in subunit-subunit interactions. Although the overall structure of TRPV3-ARD is similar to that of ARDs from other members of the TRPV subfamily, TRPV3 exhibits a unique bent finger 3 loop that is stabilized by hydrogen bonds and hydrophobic packing. This loop is not as flexible as those in other known TRPV-ARD structures, including TRPV1, TRPV2, TRPV4, and TRPV6 (Jin et al., 2006; McCleverty et al., 2006; Lishko et al., 2007; Phelps et al., 2008; Auer-Grumbach et al., 2010; Inada et al., 2012).

Chemical Activation and Inhibition of TRPV3

Since TRPV3 was discovered, a number of natural and synthetic compounds targeting TRPV3 have been identified (Table 1). However, all of the known compounds are non-specific and their effective concentrations are relatively high. Among these compounds, 2-aminoethoxydiphenyl borate (2-APB) is the most commonly used activator of TRPV3 and, to a lesser extent, TRPV1 and TRPV2, but this compound does not activate TRPV4, TRPV5, and TRPV6 (Hu et al., 2004). 2-APB also inhibits the activation of TRPM8 and TRPC6 evoked by menthol and 1-oleoyl-2-acetyl-*sn*-glycerol, respectively (Hu et al., 2004). It was initially reported that 2-APB functions as an inositol trisphosphate receptor inhibitor; it was subsequently shown to also block store-operated Ca^{2+} channels (Ma et al., 2000). The action of 2-APB on TRP channels is complicated, in that it also causes an inhibition of TRPV3 at higher concentrations ($>300\ \mu\text{M}$) (Hu et al., 2004). Similarly, it was reported that some 2-APB analogs are either activators or inhibitors of TRPV3 (Deering-Rice et al., 2014). The sensitivity of mouse TRPV3 to 2-APB, but not to camphor or voltage, is critically determined by a cytoplasmic N-terminal residue (H426) and a C-terminal residue (R696) in the channel (Hu et al., 2009).

Some natural plant products, such as camphor, eugenol, carvacrol, thymol, menthol, cinnamaldehyde, and citral, can activate TRPV3 (Xu et al., 2006; Stotz et al., 2008; Sherkheli et al., 2009, 2013; Earley et al., 2010; Ortat et al., 2012; Klein et al., 2013). The majority of these natural compounds are commonly known as flavoring ingredients, allergens, and/or skin sensitizers. Besides activating TRPV3 directly, 2-APB even at subthreshold concentrations also promotes TRPV3 current sensitization to heat (Chung et al., 2004). Likewise, TRPV3 can be potentiated or sensitized by unsaturated fatty

TABLE 1
Known compounds targeting TRPV3 channels

Compound	Activate	Inhibit	Description/Use	Reference
2-APB	TRPV1/TRPV2/TRPV3/TRPV6	TRPC6/TRPM8	Inhibitor of store-operated Ca^{2+} influx and IP_3 -mediated Ca^{2+} release; common regulator of TRP channels	Chung et al., 2004; Hu et al., 2004
Camphor	TRPV1/TRPV3	TRPA1	Modulate sensations of warmth in humans	Moqrich et al., 2005; Xu et al., 2005
Menthol	TRPV3/TRPM8/TRPA1	TRPA1	Cooling effect; modulation of warm sensation	Macpherson et al., 2006
Cinnamaldehyde	TRPV3/TRPA1	TRPM8	Used as a spice	Macpherson et al., 2006
Carvacrol	TRPV3/TRPA1		Rapidly desensitizes TRPA1; present in oregano, which is used as a spice	Xu et al., 2006
Eugenol	TRPV3/TRPA1		Present in clove, which is used as a spice; lingual irritation; innocuous warmth and pain in response to heat	Schöll and Jensen-Jarolim, 2004; Xu et al., 2006
Thymol	TRPV3/TRPA1/TRPM8		Derived from thyme, which is used as a spice	Xu et al., 2006
Incensole acetate	TRPV3		A novel anxiolytic and antidepressive agent	Moussaieff et al., 2008
FPP	TRPV3		First identified endogenous TRPV3 activator; causes nociception	Bang et al., 2010
IPP		TRPV3/TRPA1	Endogenous inhibitor; a precursor molecule for FPP synthesis in the mevalonate pathway	Bang et al., 2011
Drofenine	TRPV3		Antispasmodic agent; 2-APB analog; improved selectivity for TRPV3	Deering-Rice et al., 2014
DPBA	TRPV1/TRPV2/TRPV3/TRPV4	TRPV1/TRPV2/TRPV3	2-APB structural analogs	Chung et al., 2005
DPTHF		TRPV2/TRPV4	2-APB structural analogs	Chung et al., 2005
Nicotinic acid	TRPV1/TRPV3		Used to treat dyslipidemias but causes a side effect of cutaneous vasodilation, commonly called flushing	Ma et al., 2015
17R-RvD1		TRPV3	Proresolving lipid	Bang et al., 2012
Icilin	TRPM8	TRPV3	Super cooling agent	Sherkheli et al., 2012

DPBA, diphenylboronic anhydride; DPTHF, diphenyltetrahydrofuran; FPP, farnesyl pyrophosphate; IP_3 , inositol trisphosphate; IPP, isopentenyl pyrophosphate.

acids as well as by cholesterol (Hu et al., 2006; Klein et al., 2014). We also found that glycolic acid can strongly activate the TRPV3 channel (Cao et al., 2012). This activation is mediated by intracellular protons that act on residue H426, located at the distal N terminus, which is the same site shown to be important for 2-APB action on TRPV3 (Cao et al., 2012). Other cytoplasmic residues in TRPV3, such as L508, D512, S518, or A520, have also been reported to play a role in proton sensing (Fig. 2) (Gao et al., 2016). This novel gating mechanism, in which TRPV3 is directly activated by intracellular acidification, likely explains the cosmetic effect of α -hydroxyl acids on keratinization of the skin (Cao et al., 2012).

To date, there is a lack of specific TRPV3 antagonists, although there are several TRPV3 antagonists including the anti-inflammatory lipid mediator 17(*R*)-resolvin D1 (17R-RvD1) (Bang et al., 2012), the 2-APB structural analog diphenyltetrahydrofuran (Chung et al., 2005), the TRPM8 agonist icilin (Sherkheli et al., 2012), and isopentenyl pyrophosphate (Bang et al., 2011). However, these TRPV3 antagonists are not specific. Nevertheless, a number of TRPV3 modulators are currently under development as possible therapeutic agents with potential use in conditions including psoriasis, itch, dermatitis, hirsutism, and pain. Therefore, it is necessary to identify selective TRPV3 modulators (agonists or antagonists) that can be used either as tools to study the channel physiology or as lead compounds for validation of TRPV3 as a therapeutic target in the treatment of itch or skin-related diseases.

Regulation and Gating of TRPV3

TRPV3 is shown to be sensitized by repetitive ligand stimulations (Xu et al., 2002; Xiao et al., 2008a). Both extracellular and intracellular calcium ions play an important role in TRPV3 sensitization to repetitive stimulations by 2-APB or other stimuli, causing a slow activation at positive potential and a strong deactivation at negative potentials (Xiao et al., 2008a). The sensitization of TRPV3 to repetitive stimuli is likely dependent on a reduction of extracellular Ca^{2+} that binds to residues such as Asp641 at the pore loop, since conserved acidic residues at the equivalent positions of rat TRPV1 (Asp646) and mouse TRPV4 (Asp682) seem to play a major role in binding to divalent cations and are vital for the inhibitory activity of ruthenium red (García-Martínez et al., 2000). More interestingly, the sensitization of TRPV3 to repetitive ligand stimulations can be abolished by calmodulin (CaM) inhibitors such as calmidazolium, ophiobolin A, and W-7 (N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide hydrochloride), suggesting that Ca^{2+} -CaM is significant in maintaining the low activity of TRPV3 and that the calcium-dependent inhibition of TRPV3 function is attenuated upon repetitive stimulation (Xiao et al., 2008a).

It has been shown that ATP can interact with TRPV1-ARD (Lishko et al., 2007). The similar nucleotide specificities of TRPV1-ARD, TRPV3-ARD, and TRPV4-ARD suggest that ATP may interact with ARD domains at a conserved binding site. Two residues in TRPV3, Lys169, and Lys174, also conserved in the ATP/CaM binding on the ARD of TRPV1,

Fig. 2. A proposed model for overactive TRPV3 function or activation of TRPV3 by intracellular protons that leads to cell death and skin diseases. Schematic structure of overactive TRPV3 protein with multiple gain-of-function mutations identified from Olmsted syndrome. The solid circles in red represent dominant mutations Asn415_Arg416insLeuAsn, Gly573Cys, Gly573Ser, Gly573Ala, Gln580Pro, Leu673Phe, Trp692Phe, and Trp692Cys (Lin et al., 2012), whereas the green triangles are recessive mutations Gln216-Gly262Del, Trp521Ser, and Gly568Cys (Duchatelet et al., 2014). Weak acids can diffuse, in the protonated form, across the cell membrane and subsequently re-equilibrate to release a free proton, leading to intracellular acidification and activation of TRPV3. Protons also can pass through activated TRPV3 or other proton-permeable channels to result in intracellular acidification and activation of TRPV3. The activation of TRPV3 mediates Ca^{2+} influx and induces Ca^{2+} overload in the cytoplasm, leading to keratinization and cell death or skin diseases (Cao et al., 2012). ANK, ankyrin.

have been described to be important for interactions of TRPV3 ARD with ATP and Ca^{2+} -CaM. The binding by ATP to TRPV1 attenuates desensitization. Intriguingly, the effect is the opposite for TRPV3, where ATP reduces TRPV3 sensitivity to activators and abolishes the sensitization of TRPV3 in response to repetitive 2-APB stimulation (Phelps et al., 2010).

Under certain pathologic conditions, such as type 2 diabetes mellitus, Mg^{2+} deficiency results in skin disorders (Chutia and Lynrah, 2015). Luo et al. (2012) reported that TRPV3 is inhibited by intracellular or extracellular Mg^{2+} in primary epidermal keratinocytes, and they identified two acidic residues (E679, E682) located in the inner pore region or a residue (Asp641) from the extracellular pore loop that are critical for TRPV3-mediated signaling (Luo et al., 2012). Their findings suggest that there is a tonic inhibition of epidermal TRPV3 by both intracellular and extracellular Mg^{2+} , such that Mg^{2+} deficiency may cause TRPV3 sensitization for pathogenesis of multiple skin diseases (Luo et al., 2012).

As a common modulator for ion channels in the plasma membrane, phosphatidylinositol 4,5-bisphosphate (PIP_2) regulates TRPV3 activity in primary keratinocytes of human skin or HEK293 cells expressing TRPV3. Two residues, Arg696 and Lys705, in the TRP domain of TRPV3 were shown to be responsible for the inhibition of TRPV3 channel function by PIP_2 that reduces the open probability of the channel (Doerner et al., 2011). Breakdown of PIP_2 , in response to the activation of GPCRs that stimulate phospholipase C, causes a large shift of activation voltage from 60 to 100 mV, leading to the potentiation of TRPV3 function (Doerner et al., 2011). The PIP_2 -mediated modulation of TRPV3 channel suggests an interesting mechanism underlying its regulation by keratinocyte signaling cascades that drive cell proliferation and secretion of paracrine and autocrine factors (Doerner et al., 2011). Through this mechanism, activating Gq/11-mediated signaling can potentiate the function of TRPV3 (Xu et al., 2006).

Role of TRPV3 in Skin Physiology

TRPV3 is most abundantly expressed in the skin keratinocytes. Several lines of evidence suggest a critical involvement of TRPV3 in cutaneous sensations, hair development, and barrier function (Cheng et al., 2010; Aijima et al., 2015; Duchatelet and Hovnanian, 2015).

Cutaneous Pain. Similar to the situation seen with itch, epidermal keratinocytes modulate the process of pain sensation (Bang et al., 2011, 2012; Huang and Chung, 2013). TRPV3-coupled signaling mechanisms may play a crucial role in cutaneous nociception in epidermal keratinocytes. Indeed, compared with wild-type controls, keratinocytes overexpressing TRPV3 exhibit larger currents as well as augmented release of prostaglandin E2 (PGE2), an algogenic and proinflammatory intercellular messenger, that in turn activates adjoining sensory afferents (Huang et al., 2008; Saito et al., 2011). In keratinocytes, TRPV3 activation or stimulation also results in the release of ATP, another algogenic substance that might be considered as a keratinocyte-derived candidate nociceptive messenger molecule (Mandadi et al., 2009; Gifford et al., 2012). Finally, it is also shown that TRPV3-mediated release of nitric oxide from keratinocytes promotes wound healing and induces pain (Yoshida et al., 2006; Miyamoto et al., 2011).

As further evidence, the ability of endogenous TRPV3 modulators to reduce pain may indicate that TRPV3 mediates the nociceptive role of keratinocytes. Both 17R-RvD1, a pro-resolving lipid mediator, and isopentenyl pyrophosphate can effectively reduce inflammatory pain induced by the intradermal injection of complete Freund's adjuvant in mice, whereas farnesyl pyrophosphate causes an acute irritative response (Bang et al., 2011). In addition, silencing of TRPV3 by small hairpin RNA in epidermal keratinocytes significantly abolishes these effects (Bang et al., 2010). Certain TRPV3 antagonists are now under development in clinical phase I and II clinical trials as potential analgesic agents. Therefore, TRPV3 is apparently a novel and promising target for

analgesic therapeutic approaches. However, there are numerous questions that should be addressed in this regard: 1) Why do TRPV3-knockout mice show strong deficits in responses to innocuous and noxious heat, as well as itch, but not in pain sensation? 2) In primates, what is the function of TRPV3 expressed in DRG neurons?

Hair Growth. Hair morphogenesis is controlled by numerous growth factors that modulate the proliferation and differentiation of keratinocytes. In mice, the phenotype of wavy hair results from loss-of-function mutations occurring naturally in the transforming growth factor- α (TGF- α) and epidermal growth factor receptor (EGFR) genes, whereas upregulation of TGF- α /EGFR signaling leads to the hairless phenotype (Schneider et al., 2008). Interestingly, TRPV3 knockout also gives rise to phenotypes of curly whiskers and wavy hair coat in mice (Moqrich et al., 2005). On the contrary, DS-Nh mice and WBN/Kob-Ht rats, with a gain-of-function mutation, exhibit a hairless phenotype (Xiao et al., 2008b). It has been shown that TRPV3 is critical for the appropriate development of hair in rodents, as the channel forms a signaling complex with TGF- α /EGFR that affects hair follicle cycling and hair morphogenesis (Cheng et al., 2010). TRPV3 activation inhibits human hair growth in an assay using cocultures of human outer root sheath keratinocytes and human organ-cultured hair follicles (Borbíró et al., 2011). In addition, small interfering RNA-mediated silencing of TRPV3 effectively abrogates the cellular effects induced by TRPV3 agonists, including functional currents, reduced proliferation, elevated concentration of intracellular calcium, and apoptosis (Borbíró et al., 2011). Collectively, those findings support the notion that TRPV3 signaling is a significant factor in regulating hair growth.

Skin Barrier Formation. Skin, the largest organ in the body, functions as a protective barrier for survival of mammals. In mice, TRPV3 expression in keratinocytes contributes to skin barrier formation and maintenance. It has been shown that the skin of newborn mice lacking TRPV3 exhibits erythroderma (red color) and is scaly and dry, matching the phenotype of defective skin barrier formation in mice (Cheng et al., 2010). The mechanism is likely that activation of EGFR enhances TRPV3 channel activity, thus stimulating the release of TGF- α and TGF- α subsequently activating EGFR and then resulting in skin barrier formation. Consistent with this, TRPV3 activation by temperatures from 36 to 40°C can facilitate barrier recovery after mechanical skin barrier disruption (Denda et al., 2007). However, the human relevance of these findings needs to be investigated.

Role of TRPV3 in Skin Inflammation

Atopic dermatitis (AD), one of the most common inflammatory conditions of the skin, has similar characteristics with the phenotype of mice with a gain-of-function TRPV3 mutation (Gly573Ser) that causes a spontaneously developing dermatitis as well as a hairless phenotype (although at much lower penetrance) (Yamamoto-Kasai et al., 2013). In addition, transgenic overexpression of the TRPV3 channel Gly573Ser mutant in mouse keratinocytes leads to skin inflammation, pruritus, hyperkeratosis, immune cell infiltration, upregulation of cutaneous nerve growth factors, and systemic symptoms with increased proinflammatory cytokines and plasma IgE; together, this phenotype closely resembles the clinical

symptoms of human AD (Imura et al., 2009). A genetic study shows that the same Gly573Ser mutation also contributes to the development of hapten-induced dermatitis (Takaoka et al., 2006; Yamamoto-Kasai et al., 2013). Furthermore, TRPV3 agonists (eugenol, 2-APB) or heat activation of TRPV3 in cultured keratinocytes induces the release of PGE2 and proinflammatory interleukin-1 α . Interestingly, a number of endogenous proinflammatory molecules (including release of bradykinin, histamine, PGE2, or ATP), receptor-coupled hydrolysis of PIP₂, and activation of protein kinase C ϵ can sensitize TRPV3 to warm temperatures, resulting in an autocatalytic and TRPV3-augmented cutaneous inflammation or development of thermal hyperalgesia (Huang et al., 2008; Phelps et al., 2010).

Evidence for a proinflammatory role of TRPV3 activity in chemical nociception in the periphery of rodents is provided by the effects of 17R-RvD1, a naturally occurring lipid mediator that inhibits TRPV3-mediated activity at nanomolar to micromolar concentrations, and also reverses the thermal hypersensitivity occurring during an inflammatory response (Bang et al., 2012). TRPV3 expression is upregulated in dermal cells isolated from rosacea, a common chronic inflammatory skin disease, further supporting the important role of the TRPV3 channel in cutaneous inflammation (Sulk et al., 2012).

Identification of Gain-of-Function Mutations in Human TRPV3 That Cause Olmsted Syndrome Characterized by Severe Itching and Keratoderma

Chronic itch is a predominant and common symptom of many cutaneous disorders (e.g., atopic eczema), various systemic conditions (e.g., liver failure and end-stage renal disease), and certain neurologic and psychiatric diseases (Liu et al., 2009). Chronic itch involves a number of targets, molecules, cells, and circuits that can trigger acute and chronic itch transmission in the peripheral and central nervous systems (Bautista et al., 2014). The existing lines of evidence suggest that keratinocytes function as the “first pruriceptive transducers” and play a crucial role in cutaneous itch sensation. It has also been suggested that TRPV3 is a possible therapeutic target in pruritus (Yamamoto-Kasai et al., 2012). DS-Nh mice (Gly573 mutated to Ser) and WBN/Kob-Ht rats (Gly573 mutated to Cys) are spontaneous hairless mutant strains in rodents that develop AD-like dermatitis under normal conditions, but not under specific pathogen-free conditions (Asakawa et al., 2006; Yoshioka et al., 2009). In rodents, spontaneous dermatitis conditions share very similar characteristics that include the following (Asakawa et al., 2006; Imura et al., 2007): 1) *Staphylococcus aureus* can be isolated from skin lesions, 2) levels of serum interleukin-4 and IgE are increased significantly, 3) CD4-bearing T cells and whole mast cells are increased significantly, and 4) hyperkeratosis is observed in skin lesions with dermatitis. In DS-Nh mice expressing an overactive TRPV3 mutant, expression of thymic stromal lymphopoietin, a pruritogen, is increased in keratinocytes (Wilson et al., 2013; Yamamoto-Kasai et al., 2013), indicating that TRPV3 is a dendritic cell modulator that plays a critical role in the development of allergic dermatitis. One group has shown that

Gly573 to Ser (Nh mutation) and Gly573 to Cys (Ht mutation) are linked to hairless phenotypes and spontaneous dermatitis in mice and rats; these are two gain-of-function mutations of the *trpv3* gene at a single site that cause the channel to be constitutively open (Xiao et al., 2008b).

A TRPV3-knockout experiment has indicated that TRPV3 is involved in pruritus (Yamamoto-Kasai et al., 2012). The mouse model of dry skin initiated by application of an acetone/ether/water (AEW) mixture to the rostral back twice a day results in histamine-independent spontaneous scratching/itch. The AEW treatment causes dry skin in both wild-type and TRPV3 knockout mice; however, spontaneous scratching is significantly increased in the AEW treated areas only in the wild-type mice, and not in TRPV3 knockout mice, demonstrating a critical role of TRPV3 in itch sensation induced by dry skin (Yamamoto-Kasai et al., 2012). However, there are some unaddressed questions: 1) If TRPV3 point mutations are responsible for the pruritus, why does no dermatitis arise on specific pathogen-free conditions? 2) Can a TRPV3-specific antagonist reduce the pruritus? 3) Why are there no reports that the TRPV3 agonists cause pruritus? 4) Is TRPV3 significantly elevated in the skin of pruritus patients? 5) Since TRPV3 is most abundantly expressed in skin keratinocytes, how is the itch information transmitted to sensory neurons?

In our collaboration with dermatologists of the Yang laboratory, three gain-of-function TRPV3 mutations from patients with Olmsted syndrome were identified. OS, also known as mutilating palmoplantar keratoderma with periorificial keratotic plaques, is a rare congenital disorder characterized by palmoplantar and periorificial keratoderma, alopecia in most cases, and severe itching (Lai-Cheong et al., 2012; Lin et al., 2012). The three gain-of-function mutations were identified from six unrelated Olmsted syndrome patients in China, in which five patients carried either the G573S (an identical mutation with the rodent) or G573C mutation, and one had a mutation at W692G (Lin et al., 2012). Whole-cell or inside-out patch clamp recordings of TRPV3 currents from HEK293 cells transfected with the TRPV3 mutants demonstrate that these mutants are constitutively open and induce large inward currents, as compared with the wild-type TRPV3 that is only an outward rectifier. The G573S or W692G mutant also elevates intracellular Ca^{2+} concentrations (Lin et al., 2012). The G573S mutation was also identified in a patient from India and new G573A, W692C, and L673F mutations and a homozygous recessive mutation W521S have also recently been reported for patients characterized by severe itching from Belgium, Iranian, France, and Israel (Duchatelet et al., 2014; Eytan et al., 2014; Kariminejad et al., 2014; Agarwala et al., 2016). Moreover, in one patient a heterozygous six-nucleotide insertion in TRPV3 gene resulted in the in-frame insertion of two additional amino acids (p.Asn415_Arg416insLeuAsn) (Agarwala et al., 2016). A similar skin disease named focal paloplantar keratoderma, which is characterized by the presence of circumscribed calluses on the palms and soles, also carries a causative mutation Q580P in a three-generation Chinese family (He et al., 2015).

Molecular considerations regarding the observed human mutations are as follows. The residue G573 is located in the linker region between transmembrane S4 and S5 segment of TRPV3 subunit, and W692 is located in the conserved TRP box (amino acid sequence of IWRLQR) of TRP domain after S6 segment in the C terminus. The S4 and S5 linker functions to

translate movement of the voltage sensor into the gating of the pore (Liao et al., 2013). The TRP box interacts with the S4–S5 linker and couples stimulus sensing to channel gating (García-Sanz et al., 2007; Cao et al., 2013; Liao et al., 2013). Therefore, the identified three mutations located in the S4–S5 linker (G573S, G573C) or TRP domain (W692G) cause a disruption of the gating coupling and lock the channel in an open conformation. The excessive Ca^{2+} influx through constitutively open gain-of-function mutations of TRPV3 leads to intolerant itching sensation and severe keratoderma with profound mast cell infiltration and histamine release in the upper dermis, as detected by skin biopsy sectioning (Lin et al., 2012). The nature of the gain-of-function mutations indicates that selectively targeting TRPV3 is likely an effective approach for the treatment of skin keratinization, hair loss, and itching disorders.

Conclusions and Perspectives

Since TRPV3 was first cloned in 2002, we have gained considerable insight into the structure, function, and modulation of the channel. TRPV3, the dominant TRP molecule in the skin, is involved in skin barrier formation and hair growth and mediates the cutaneous sensation of itch and pain. The identification of genetic gain-of-function mutations of TRPV3 from patients with Olmsted syndrome has significantly advanced our understanding of the causative role of dysfunctional TRPV3 in severe itching and skin diseases. The existing studies indicate that TRPV3 stands out as an attractive emerging target for chronic itch and itch-related skin diseases. Future efforts should be devoted to not only understand the molecular mechanism underlying TRPV3-mediated itch signaling but to also screen and identify specific TRPV3 antagonists that can selectively inhibit overactive TRPV3. Such agents could provide a platform for developing effective antipruritic therapies for chronic itch or TRPV3-related skin diseases.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: G. Wang and K. Wang.

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