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REVIEW

Role of Transient Receptor Potential Vanilloid 4 Channel in Skin Physiology and Pathology

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دور قناة مُستَقبلة فانلويد 4 ذات الجهد المؤقت في وظائف الجلد وأمراضه

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ABSTRACT: Transient receptor potential vanilloid 4 (TRPV4) channel responds to temperature, as well as various mechanical and chemical stimuli. This non-selective cation channel is expressed in several organs, including the blood vessels, kidneys, oesophagus and skin. In the skin, TRPV4 channel is present in various cell types such as keratinocytes, melanocytes and sensory neurons, as well as immune and inflammatory cells, and engages in several physiological actions, from skin homeostasis to sensation. In addition, there is substantial evidence implicating dysfunctional TRPV4 channel—in the form of either deficient or excessive channel activity—in pathological cutaneous conditions such as skin barrier compromise, pruritus, pain, skin inflammation and carcinogenesis. These varied functions, combined with the fact that TRPV4 channel owns pharmacologically-accessible sites, make this channel an attractive therapeutic target for skin disorders. In this review, we summarize the different physiological and pathophysiological effects of TRPV4 in the skin.

Keywords: TRPV4; Skin; Epidermis; Keratinocytes; Pain; Pruritis; Melanoma.

الملخص: تستجيب قناة مُسْتَقبلة فانلويد 4 ذات الجهد المؤقت للحرارة بالأضافة الى محفزات ميكانيكية وكيميائية مختلفة. توجدهذه القناة غير الانتقائية للايونات الموجبة في العديد من أعضاء الجسم ، بما في ذلك الأوعية الدموية والكلى والمريء والجلد. وفي الجلد توجد هذه القناة في أنواع مختلفة من الخلايا، مثل الخلايا الكيراتينية والخلايا الصباغية والخلايا العصبية الحسية وكذلك الخلايا المناعية والالتهابية، حيث تنخرط في العديد من الاعمال الوظيفية التي تتراوح من استتْباب الجلد إلى الإحساس. بالإضافة إلى ذلك هناك قدر كبير من الأدلة التي تشير إلى وجود اختلالات وظيفية بهذه القناة، اما على هيَئة نقص أو فرط في نشاط القناة، في حالات مرضية جلدية مثل اختلال حاجز الجلد والحكة والألم والالتهاب الجلدي والتسرطن. هذه الوظائف المتنوعة، إلى جانب حقيقة امتلاك هذه القناة لمواضع يمكن الوصول إليها دوائيا، تجعلها هدفًا جذابًا لعلاج اضطرابات الجلد. في هذا الاستعراض نلخص الآثار الوظيفية والفيزيولوجيا المرضية المختلفة لهذه القناة في الجلد.

الكلمات المفتاحية: قناة مُسْتَقبلة فانلويد 4 ذات الجهد المؤقت؛ جلد؛ بَشَرة؛ خلايا كيراتينية؛ ألم؛ حكة؛ ورم ميلانيني.

In the human body, the skin is the largest organ and is composed of three primary layers. The epidermis, the outermost superficial layer, is composed of multiple layers of keratinocytes. Basal keratinocytes divide to produce suprabasal keratinocytes that pass through several stages of differentiation and ultimately give rise to non-nucelated cells in the superficial stratum corneum. The cornified keratinocytes in conjunction with the dense intercellular structures comprise the impermeable hydrophobic skin barrier that prevents noxious substances and pathogens from getting into the human body and halts water vaporisation from the body. Melanocytes residing adjacent to the basal keratinocytes manufacture melanin and deliver it to neighboring keratinocytes. The epidermal antigen-presenting cells, known as Langerhans cells, capture exogenous and endogenous antigens and present them to the regional draining lymph nodes to provoke an immune response. The dermis, the middle layer of skin, is composed of extracellular matrix, collagen, fibroblasts, endothelial cells and mast cells. It maintains the skin through the provision of nutrients and oxygen via its extensive vascular network and is the main contributor to the physical properties of the skin as an excessive deposition of extracellular matrix, collagen and fibroblast could lead to abnormal wound healing. It also conveys the sensory nerve endings from the epidermis to the deeper layer of the skin and hosts the hair follicles. The hypodermis, the innermost layer of skin, is mainly formed of adipose tissue that functions as a heat insulator and acts as an energy storage site.[1]

As an integrative system, the skin maintains homeostasis, provides an immunological barrier, synthesises melanin pigments and plays a major role in sensation. Current evidence indicates that transient receptor potential (TRP) channels play a crucial role in mediating and adjusting these different functions.[2] Furthermore, disturbances in the expression or function

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of these channels can result in abnormal keratinocyte differentiation, skin pigmentary and inflammatory diseases and possibly carcinogenesis.

Overall, TRP channels are non-selective cation channels that mediate the influx of calcium ions (Ca^{2+}), magnesium and monovalent cations into different cells.[2] A functional TRP channel is formed of a central hydrophilic channel pore surrounded by four subunits consisting of six transmembrane protein segments with C- and N-terminals protruding into the cytoplasm.[3,4] To date, the TRP superfamily is composed of a total of 29 members divided into seven subfamilies based on amino acid arrangement, including the ankyrin, canonical, melastin, mucolipin, polycystin, no-mechanoreceptor potential and vanilloid (TRPV) subfamilies.[2,5,6] These channels are found in various tissues and organs, with almost every cell expressing at least one subtype, and engage in several physiological cellular processes, including proliferation, *apoptosis*, cell death, mechanosensation, cell volume regulation, secretion, control of vascular permeability and blood vessel tone, as well as angiogenesis.[7–11] Moreover, TRP channels can be gated by a wide range of physical and chemical stimuli such as mechanical forces, temperature and various ions and small molecules.[12,13] Seemingly, TRP channels are crucial players in multiple facets of health and ailment.[14]

Like other tissues and organs in the body, the skin expresses many different TRP subtypes that significantly influence its proliferation, growth and integrity via different mechanisms, as well as its functioning in both healthy and diseased states.[15,16] The skin has an extracellular calcium gradient, consisting of low levels near the basal keratinocytes and relatively higher concentrations around the superficial epidermal keratinocytes. Several types of TRP channels mediate calcium influx into sensory neurons, immune cells, keratinocytes and melanocytes in the skin; this potentially explains how these channels affect cellular proliferation, differentiation, cell migration, cytotoxicity and the secretion of paracrine and autocrine chemicals.[17] Calcium is of particular importance to epidermal keratinocytes as it promotes their progressive differentiation while being pushed apically by actively dividing basal cells.[18] Abnormal homeostasis of calcium, as in conditions such as Darier's disease or Hailey-Hailey disease, leads to poor adhesion between keratinocytes, disrupted epidermal differentiation, keratosis and other skin malfunctions.[19,20]

Another important function of TRP channels is their ability to cause membrane depolarisation as a result of thermal, mechanical and chemical stimuli.[2] Subsequently, TRP channel-mediated depolarisation triggers action potential firing in cutaneous sensory neurons, leading to sensations of temperature, itching and pain.[21] Furthermore, TRP channel stimulation can also depolarise non-excitable cells and alter other cellular processes, such as the release of adenosine triphosphate (ATP) from keratinocytes.[22]

The fourth member of the TRPV subfamily (TRPV4) was initially reported as an osmo- or mechanosensor that can be stimulated by moderate warmth (>27°C) and ultraviolet (UV) light, as well as stimulated or inhibited by various chemical stimuli, including GSK1016790A, the synthetic phorbol ester 4α-phorbol 12,13-didecanoate and HC-067047.[23–30] Like other subtypes, TRPV4 is expressed throughout the body including the hippocampal neurons, endothelial cells, oesophageal, gastric and urinary bladder epithelia as well as skin keratinocytes, where it contributes to numerous physiological processes.[9,10,26,30–33] Figure 1 illustrates the various functions of TRPV4 channels in different skin cells. Although several TRPV4 agonists and antagonists have been studied in animal models, none have yet been tested in human clinical trials [Table 1].[29,34–49]

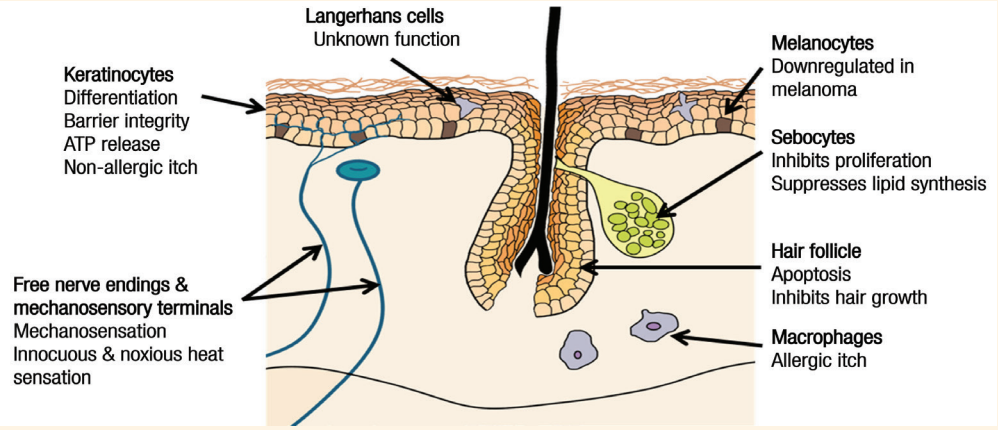

Figure 1: Diagram illustrating the functional expression of transient receptor potential vanilloid 4 channel in different skin cells.
ATP = adenosine triphosphate.

This review will discuss the functional expression of TRPV4 channel in various types of cells in the skin, as well as its contribution to different cutaneous physiological and pathological processes.

Epidermal Barrier Function

In the skin, the epidermal barrier restricts extensive epidermal water loss and prevents dehydration and noxious substances and pathogens from entering the body. This barrier function is upheld by a hydrophobic cornified layer formed of an uninterrupted sheet of keratin-rich cells enclosed in an extracellular unionised lipid layer.[50,51] Other equally indispensable structures include the intercellular junctions underneath this cornified layer, such as the *adherens* junctions (AJs) and tight junctions (TJs).[52,53]

In mice, TRPV4 is expressed in epidermal keratinocytes and its stimulation—either by temperature or selective agonists—accelerates barrier regeneration.[54,55] Moreover, TRPV4 is specifically colocalised with AJ components, mainly β-catenin and E-cadherin, at the plasma membrane of these keratinocytes, thus supporting its role in epidermal barrier homeostasis.[33] Warm temperatures provoke TRPV4-mediated Ca^{2+} influx into keratinocytes, resulting in their subsequent differentiation and cell-cell contact formation.[33] This promotes the development of an intact cell-cell junction-dependent barrier, including both TJs and AJs, and is disrupted in TRPV4-deficient mice.[33]

Thermal and chemical stimulation of TRPV4 channel also elevates intracellular calcium in human keratinocytes and contributes to the formation of intercellular junctions, thus reinforcing intercellular barrier integrity in both *ex vivo* and *in vitro* experiments, with the knockdown of this channel compromising the formation of augmented transepithelial resistance in cultures of human keratinocytes.[56] Indeed, TRPV4 activation due to warm temperatures and chemical agonists reinforces the TJ-associated barrier of human keratinocytes via the upregulation of TJ structural proteins occludin and claudin-4, and accelerates barrier function recovery in *ex vivo* human skin after cornified layer removal.[57] However, while there is evidence supporting the function of TRPV4 in skin barrier formation, its role in wound healing has not yet been elucidated.

Table 1: Animal studies involving transient receptor potential vanilloid 4 channel agonists and antagonists[29,34–49]

	Selectivity	*In vivo* (route/ species)
Agonist		
4αPDD[29,34]	Non-selective	+ (intraplantar/ mice)
PMA[29]	Non-selective	-
5,6-EET[38–40]	Non-selective	-
DMAPP[41]	Non-selective	+ (intraplantar/ mice)
BAA[42]	Non-selective	-
N-arachidonoyl taurine[43]	Non-selective	-
Apigenin[44]	Unknown	-
CBDV and THCV[29]	Non-selective	-
RN-1747[45]	Non-selective	-
GSK1016790A[29,36]	Non-selective	+ (IV, SC/mice)
Antagonist		
Gd[3+46]	Non-selective TRPV	-
La[3+46]	Non-selective TRPV	-
RR[29,46,47]	Non-selective	-
Capsazepine[48]	Non-selective TRPV	-
RN-1734[48]	Selective	-
Butamben[48]	Non-selective	-
Citral[48]	Selective	-
GSK205[37,48]	Selective	+ (topical/mice)
HC-067047[35,48]	Selective	+ (SC/mice)
GSK2193874[48,49]	Non-selective	+ (IV, IP/mice & rats)

PDD = phorbol-12,13-didecanoate; PMA = phorbol 12-myristate 13-acetate; EET = epoxyeicosatrienoic acids; DMAPP = dimethylallyl pyrophosphate; BAA = bisandrographolide A; CBDV = cannabidivarin; THCV = tetrahydrocannabidivarin; SC = subcutaneous; IV = intravenous; TRPV = transient receptor potential vanilloid; Gd3+ = gadolinium; La3+ = lanthanum; RR = ruthenium red; IP = intraperitoneal.

Sensory Functions

There is substantial evidence supporting the involvement of TRPV4 channel in the transduction of different sensory modalities. In some cases, these functions are mediated by the neurally-expressed TRPV4 channel, while in other cases these are mediated via expression in keratinocytes and other skin-residing cells.

THERMOCEPTION

The conscious or unconscious perception of atmospheric temperature is a physiological process that is pivotal for body temperature homeostasis and the avoidance of dangerous or life-threatening thermal extremes. Cutaneously, heat is perceived by free nerve endings that connect to small diameter fibres or by epidermal keratinocytes with abundant TRPV4 expression.[25,58] In

mice, warm temperatures elicit currents in primary keratinocytes, with most heat-elicited responses seemingly mediated by TRPV4.[54]

It is possible that TRPV4 participates in the Ca^{2+} homeostasis of keratinocytes in response to slight variations in skin temperature, which might in turn affect Ca^{2+}-dependent processes, such as keratinocyte proliferation and differentiation or intercellular junction formation.[59,60] On the other hand, another explanation is that TRPV4 expression in keratinocytes results in the secretion of mediators such as ATP, which in turn stimulates adjacent afferent nerve fibres and, hence, the transduction of warmth.[61–63] Additionally, TRPV4 is involved in sensations of innocuous warmth, although the effect in TRPV4-deficient mice was modest and condition-dependent, with the mice exhibiting preferences for slightly warmer temperatures during a thermal gradient assay.[64]

MECHANOSENSATION

Mechanosensation involves the transduction of mechanical stimuli into neural signals, with mechanoreceptors in the skin responsible for the sensation of touch. Both low- and high-threshold dorsal root ganglion (DRG) neurons express TRPV4 channel.[58] In addition to its expression by free nerve endings, TRPV4 is also present in cutaneous mechanosensory terminals, including Merkel nerve endings, Meissner corpuscles and intraepidermal and penicillate terminals. This distribution indicates that the sensation of pressure by TRPV4 channel is transmitted through A- and C-fibres, where it plays a role in cutaneous mechanosensation.[58] Another possibility is that TRPV4 channel in keratinocytes respond to mechanical stimuli by releasing ATP, which is subsequently recognised by the neighbouring sensory fibres that mediate mechanotransduction.[61–63]

NOCICEPTION

Nociception refers to the detection of stimuli causing pain. Significantly elevated levels of TRPV4 expression in keratinocytes have been observed among patients with breast pain, correlating with the higher expression of nerve growth factor in these keratinocytes and, hence, sensitisation of the nociceptive nerve fibres.[65] Furthermore, TRPV4 has been implicated in osmotically-evoked pain behaviours and acute mechanical nociception, as well as mechanical hyperalgesia in inflammatory and neuropathic pain.[66–76]

While TRPV4 does not contribute to the normal somatosensory detection of mechanical stimuli, it plays an important role in mechanical hyperalgesia, as it interacts with α2β1 integrin and the Src protein-tyrosine kinase to form a molecular complex that functions only in the setting of nerve injury or inflammation.[77] Additionally, kinins can sensitise TRPV4 to induce mechanical hyperalgesia, a mechanism thought to contribute to the maintenance of mechanical hyperalgesia and paclitaxel-induced chronic pain in mice; accordingly, these receptors may present potential targets for the treatment of chemotherapy-induced neuropathy.[34]

Some proalgesic factors, such as protease-activate receptor 2 agonists, also provoke mechanical hyperalgesia mediated by TRPV4 channel.[78] In diabetic mice, TRPV4 blockade by the selective antagonist HC067047 prevented the development of mechanical allodynia, an effect seemingly independent of changes in the expression level of TRPV4 in the sensory neurons.[35,79] Moreover, inflammation-induced thermal hyperalgesia is reportedly impaired in TRPV4-deficient mice.[80]

Sunburn-Associated Hyperalgesia

Additionally, TRPV4 is involved in hyperalgesia associated with sunburn. Exposure to UVB rays induced a TRPV4-mediated calcium influx into cultured mouse keratinocytes, with the subsequent release of endothelin (ET)-1, a pruriceptive/nociceptive peptide.[81] Furthermore, UVB-induced inflammation, as well as thermal and mechanical hyperalgesia, are reduced in TRPV4-deficient mice or those treated with TRPV4 channel blockers.[81] Following sunburn, knocking out keratinocyte-specific TRPV4 in mice curtailed the secretion of proinflammatory factor interleukin (IL)-6, consequently decreasing the numbers of recruited neutrophils and macrophages.[81]

Similarly, TRPV4 immunoreactivity is increased in human skin after exposure to UVB rays.[81] A recent study found that γ-irradiation of keratinocytes prompted TRPV4-mediated ATP release, thereby stimulating the P2Y11 receptor and resulting in the release of IL-6 and IL-8 via the p38 mitogen-activated protein kinase (MAPK)-nuclear factor-κB signalling pathway.[82] Therefore, as both TRPV4 and ET-1 apparently play a role in acute photodermatitis in humans, TRPV4 channel may be a potential curative target for UVB- and γ irradiation-induced dermatitides.[82]

PRURITUS

Chronic itching is a major clinical symptom in many skin disorders. Itch-sensitive neurons are stimulated by a wide range of exogenous itch-causing compounds (i.e. pruritogens). Additionally, keratinocytes and skin-resident immune cells have the ability to release endogenous pruritogens—including ATP, ETs, prostaglandins, histamine, nitric oxide and serotonin—which can directly activate or sensitize the primary sensory neurons and cause itching, thus implying that the skin plays a role in the inception of itching sensations.[83,84] In both humans and mice, several TRP channels are

key mediators of itching sensations as they directly activate the peripheral pruriceptors or mediate the release of pruritogens from keratinocytes and other skin-resident cells.[84–86]

The involvement of TRPV4 in the sensation of itching is supported by a growing amount of data; for instance, in mice, the subcutaneous injection of GSK1016790A, a TRPV4 agonist, induced itch-related behaviours.[36] Moreover, TRPV4 contributes to histamine- and serotonin-induced acute itching, although its exact role is uncertain.[87] An intradermal injection of serotonin in TRPV4-deficient mice induced significantly less scratching compared to wild-type controls.[88] Serotonin-induced itching is also suppressed by the pharmacological inhibition of TRPV4 or 5-hydroxytryptamine (HT)-2 receptor, suggesting that 5-HT2-mediated itching is interceded by a downstream TRPV4-dependent pathway.[88] On the other hand, scratching behaviours evoked by histamine injection reportedly differ little between TRPV4-deficient and wild-type mice.[88]

In a murine model of chronic itching, TRPV4 activation promoted downstream 5-HT signalling, with TRPV4-expressing keratinocytes and dermal macrophages involved in non-allergy- and allergy-related chronic itching, respectively.[89] Moreover, scratching behaviours evoked by all histaminergic pruritogens (including histamine, ET-1 and compound 48/80) were significantly diminished in keratinocyte-specific, tamoxifen-induced TRPV4-deficient mice; moreover, the topical application of a TRPV4 blocker, GSK205, on wild-type mice also reduced scratching reactions evoked by these pruritogens.[37]

These findings indicate that TRPV4 channel plays a role in histaminergic itching. Histamine induces a TRPV4-dependent Ca^{2+} influx into the keratinocyte through the histamine H1, H3 or H4 receptors, resulting in the phosphorylation of MAPK and extracellular signal-regulated kinase (ERK), and triggering signalling of the itching sensation.[37] However, it is not clear if topically-applied inhibitors of TRPV4, histamine receptors or MAPK/ERK signalling pathways also act on cutaneous sensory nerve endings in addition to skin-resident cells. Besides the phenotypic differences, whether TRPV4 expression in the skin or the DRG neurons is the main mediator of itch is still an open question; Akiyama *et al*. proposed that serotonin-evoked scratching was mediated by TRPV4 functionally expressed in DRG neurons, whereas Chen *et al*. theorised that histaminergic itching was mediated by TRPV4 expressed in epidermal keratinocytes.[37,88]

Chloroquine (CQ) is another well-established pruritogen which can be used to induce acute histamine-independent itch model in mice. Interestingly, two studies reported different outcomes with regards to CQ-elicited itching in TRPV4-null mice; in the first, CQ-elicited itching was significantly elevated in TRPV4-deficient mice in comparison with wild-type mice, whereas the other study found that CQ-induced scratching was not affected in TRPV4-deficient mice.[37,88] Therefore, the exact role of TRPV4 in mediating acute itching warrants further research.

Regulation of Hair Follicle Cycle

A recent study reported TRPV4-positive immunoreactivity in intact human hair follicles during the anagen growth phase, with immunoreactivity detected in the cortex of the bulbar hair shaft as well as the inner and outer root sheath layers of the hair follicle epithelium.[90] Moreover, *in vitro* TRPV4 activation increased the number of apoptotic cells in areas with matrix keratinocytes and inhibited hair elongation, suggesting a regulatory role in hair follicle cycling.[90]

Role in Skin Diseases

An overview of the contribution of TRPV4 to different cutaneous diseases and its potential role in treatment is shown in Table 2.[33,55,57,81,91–100]

NON-MALIGNANT DISEASES

Acne *vulgaris* is one of the most common skin diseases in humans and is characterised by the overproduction of sebum, unwanted sebocyte proliferation and inflammation.[101] In human sebocytes, TRPV4 is functionally expressed and its activation exerts both lipostatic and antiproliferative effects.[91] As such, TRPV4 could be potentially beneficial in acne treatment. Additionally, several genetic TRPV4 mutations reportedly cause Charcot-Marie-Tooth disease type 2C, a hereditary neurodegenerative disease associated with sensorimotor neuropathy.[92–94]

Rosacea is a chronic dermatitis that is accompanied by neurogenic inflammation. Compared with healthy skin, different types of *rosacea* display elevated expressions of different TRPV channels (including TRPV4), at either the molecular or protein levels, suggesting that TRPV dysregulation may be an important mechanism underlying the initiation and maintenance of this condition.[95] Additionally, TRPV4 expression is elevated in both Langerhans and dermal cells in *rosacea* and can be stimulated under inflammatory conditions and by *rosacea*-related factors; accordingly, TRPV4 could be involved in the underlying inflammation in *rosacea*.[95] A recent study revealed that TRPV4 is a key driver for

Table 2: Potential role of transient receptor potential vanilloid 4 channel in various skin diseases[33,55,57,81,91–100]

Disease	Involvement of TRPV4	Potential therapeutic benefit
Barrier-related diseases	• Activation induces barrier recovery and promotes the tight-junction barrier between keratinocytes.[55,57,99] • Genetic deletion is associated with leaky cell-cell junctions.[33,100]	• Potentially beneficial for treating skin barrier comprise and inducing barrier recovery.
UV-induced skin diseases	• Involved in hyperalgesia associated with sunburn.[81]	• A potential curative target for UVB-induced and γ irradiation-induced dermatitides.
Acne *vulgaris*	• Activation inhibits sebocytes proliferation and suppresses lipid synthesis.[91]	• Could have potentially curative properties.
Rosacea	• Mediates mast cell activation. • Reduces expression dysregulation.[95]	• Inhibition could have potentially curative properties.
Charcot Marie Tooth disease (type 2C)	• Several TRPV4 mutations produce neurodegenerative condition including dry skin and hair loss.[92–94]	-
Malignant melanoma	• Mediates cell *apoptosis* with decreased expression.[96–98]	• Could be utilised as an early diagnostic or prognostic marker. • Activation could have potentially curative properties.

TRPV4 = transient receptor potential vanilloid 4; UV = ultraviolet.

mast cell-mediated skin inflammation in *rosacea*.[102]

MALIGNANT AND PREMALIGNANT DISEASES

Although TRPV4-related immunoreactivity and messenger ribonucleic acid transcripts are maintained at high levels in healthy or inflamed skin, they are abrogated in keratinocytic tumours. In both premalignant lesions and non-melanoma skin cancers, TRPV4 is markedly downregulated or even absent, seemingly as a result of the release of keratinocyte-derived IL-8, suggesting that the selective downregulation of TRPV4 appears to be an early diagnostic marker of skin carcinogenesis.[96]

Moreover, in human melanoma A375 cell lines, TRPV4 stimulation suppresses cell proliferation and induces cell *apoptosis*.[97] A recent study revealed that TRPV4 stimulation, with calcium signalling involvement, mediates human melanoma A375 cell death by regulating the Akt pathway-driven antitumour process.[98] While the involvement of TRPV4 in tumourigenesis has yet to be fully explored, these findings suggest that TRPV4 expression might serve as a prognostic or early diagnostic biomarker in human melanomas, while TRPV4 activation could even hold potentially curative properties.[98]

Conclusion

Overall, TRPV4-mediated processes are not only limited to sensory functions, such as itching and pain, but also play a crucial role in keratinocyte proliferation and differentiation as well as skin barrier formation, maintenance and regeneration. Therefore, modifying TRPV4 function could improve skin barrier function, especially in conditions where there is a breach in the cornified layer-dependent barrier. Moreover, TRPV4 channel may be involved in certain diseases, thus providing possibilities for therapeutic targeting. For example, TRPV4 inhibition could help in the treatment of UVB-induced inflammation and acne *vulgaris*, whereas TRPV4 activation or upregulation could be of therapeutic value in the treatment of both melanoma and non-melanoma skin cancers.

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