



Transient Receptor Potential Vanilloid1 (TRPV1) Channel Opens Sesame of T Cell Responses and T Cell-Mediated Inflammatory Diseases

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Transient receptor potential vanilloid1 (TRPV1) was primarily expressed in sensory neurons, and could be activated by various physical and chemical factors, resulting in the flow of extracellular Ca²⁺ into cells. Accumulating data suggest that the TRPV1 is expressed in some immune cells and is a novel regulator of the immune system. In this review, we highlight the structure and biological features of TRPV1 channel. We also summarize recent findings on its role in modulating T cell activation and differentiation as well as its protective effect in T cell-mediated inflammatory diseases and potential mechanisms.

Keywords: TRPV1, T cell, Ca²⁺, fever, T cell-mediated inflammatory diseases

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INTRODUCTION

Transient receptor potential (TRP) is a large superfamily of nonselective cation channels comprising of 28 members mainly located on the cell membrane. The TRP superfamily can be divided into TRPC (Canonical/Classical), TRPV (Vanilloid) and TRPM (Melastatin) sub-families (1). TRPV sub-families can be activated by vanillic acid compounds consisting of TRPV 1-6 (2). In 1997, TRPV1 was identified as a receptor of capsaicin, the main pungent component in “hot” chilli pepper (3). Over the past few decades, TRPV1 has been widely studied in the nervous system. In the peripheral nervous system, TRPV1 channel was found to be highly expressed in the spinal dorsal root ganglion neurons, the trigeminal ganglion and primary sensory neurons, which mainly mediate pain perception, transmission and regulation process. In the central nervous system, the TRPV channel was mainly involved in the regulation of body temperature, release of synaptic neurotransmitters, synaptic transmission and apoptosis (4). In addition, recent studies have revealed that TRPV1 was widely expressed in non-neuronal cell membranes of the kidney, pancreas, testes, uterus, spleen, stomach, small intestine, lung and liver mucous gland (2). Besides, the TRPV1 channel has been shown to play an important role in the immune system.

In this review, we discuss the structure and biological characteristics of the TRPV1 channel and highlight recent findings on the roles of the TRPV1 channel in controlling T cell activation and differentiation. We also discuss the protective functions of the TRPV1 in T cell-mediated inflammatory diseases and the underlying potential mechanisms.

THE STRUCTURE AND BIOLOGICAL CHARACTERISTICS OF THE TRPV1 CHANNEL

TRPV1 channel is a coding protein with a molecular weight of 95 kDa, composed of 838 amino acids. Sequence analysis data has shown that the TRPV1 channel is a homologous tetramer composed of four subunits, each of which has six-transmembrane domains with a pore-forming hydrophobic group between the fifth and sixth transmembrane domains (5). Its N-terminal and C-terminal regions are located in the inner side of the cell membrane to regulate the receptor functions. The N-terminal contains several phosphorylation sites and six ankyrin repeat domains, which bind calmodulin and ATP and modulate the sensitivity and functions of the TRPV1 (6, 7). On the other hand, the C-terminal bears a TRP domain, multiple calmodulin binding domains and endogenous substance binding sites, such as phosphatidylinositol-4,5-bisphosphate (PIP₂) (8, 9) (**Figure 1**).

The TRPV1 is a multimodal receptor, which is activated and/or allosterically modulated by a range of thermal, mechanical and chemical stimuli (11). Besides capsaicin, TRPV1 channel is also activated by a variety of other plant-derived vanilloids, including camphor and resiniferatoxin (RTX), and putative endogenous vanilloids such as the endocannabinoid, inflammatory mediators such as arachidonic acid (12, 13). The thermal sensitivity of the TRPV1 was shown to be enhanced by various pro-inflammatory factors, such as nerve growth factor (NGF), bradykinin, lipid, prostaglandin and ATP (14). Although many studies have evaluated the role of PIP₂ in the activation of TRPV1, the data still remains controversial. For instance, Yao et al. demonstrated that PIP₂ could fuel the activation of TRPV1 (15, 16), while other studies reported that PIP₂ inhibited the TRPV1 activation (17, 18). Since the membrane is a highly asymmetric lipid bilayer, the contradictory effects of PIP₂ on

the TRPV1 may be depending on which leaflet of the cell membrane it interacts with. Insertion of the PIP₂ into the inner leaflet of the plasma membrane enhanced the response of capsaicin in activating the TRPV1, while insertion into both leaflets suppressed the channel activation (19). Other activators of the TRPV1 channel include heat (>43 °C), low pH (< 5.4), static charge and voltage change (13). It has been demonstrated that TRPV1 is intrinsically heat sensitive (18), and temperature sensing is associated with voltage-dependent gating in the heat-sensitive channel TRPV1 (20).

After the TRPV1 activation, extracellular Ca²⁺ flows into the cells, and the intracellular the Ca²⁺ pool releases, resulting in increased concentration of intracellular Ca²⁺ (21). This increased intracellular Ca²⁺ mediates the basic activities of many cells, such as muscle contraction, neuronal activity, transmitter release, cell proliferation and apoptosis. In addition, activated TRPV1 can regulate body temperature and pain (22, 23).

THE ROLE OF THE TRPV1 CHANNEL IN T CELL RESPONSES

Functional Expression and TCR-Mediated Activation of TRPV1 in CD4⁺ T Cells

Some previous studies analyzed the expression of TRPV1 mRNA and protein in human peripheral blood mononuclear cells (PBMC) (24), and found that they were expressed in mouse and rat thymocytes (25, 26). Thereafter, other studies demonstrated the expression of TRPV1 on human NK and CD3⁺ T cells (27, 28), as well as in primary mouse and human T cells and human T cell line (Jurkat cells) (24, 28–32). Thus, the TRPV1 channel might play a pivotal role in T cells.

The activation and function of TRPV1 could be modulated by TCR-induced signaling pathway. In resting and TCR-stimulated

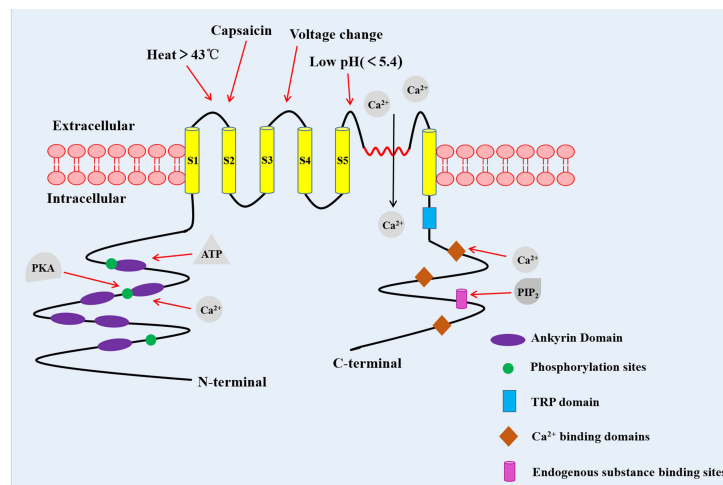


FIGURE 1 | The structure of the TRPV1 channel. TRPV1 channel is a homologous tetramer composed of four subunits, with six-transmembrane domains and a pore-forming hydrophobic group between the fifth and sixth transmembrane domains. The N-terminal contains several phosphorylation sites and six ankyrin repeat domains. The C-terminal has a TRP domain, multiple calmodulin binding domains and binding sites of endogenous substance. PKA, Protein kinase A (10).

CD4⁺ T cells, TRPV1 binds TCR co-receptor CD4 and Src-family tyrosine kinase Lck (33). The tyrosine of TRPV1 was rapidly phosphorylated by Lck in response to TCR stimulation leading to inactivation of TRPV1, which was not modified in Lck-deficient T cells (33). In addition, PIP₂ in the intracellular leaflet of the plasma membrane was shown to activate TRPV1. In contrast, PIP₂ located in both leaflets suppressed the activation of the TRPV1 (19). PIP₂ was hydrolyzed into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃) by TCR-induced activated phospholipase C gamma 1 (PLC-γ1) (33). The hydrolysis of PIP₂ relieved the PIP₂-mediated inhibition of the TRPV1 (16). Besides, IP₃ binds to its receptor (IP₃R) on endoplasmic reticulum (ER), contributing to the release of Ca²⁺ from the intracellular Ca²⁺ pool (33) (Figure 2).

The TCR Signals and TRPV1 Increase Ca²⁺ in CD4⁺ T Cells

The elevation of intracellular Ca²⁺ is required for T cell activation, proliferation, differentiation and effector functions (34). The engagement of TCR increases the intracellular Ca²⁺ concentration, which results from a dual Ca²⁺ response; Ca²⁺ release from the ER stores and Ca²⁺ influx from the extracellular milieu into the cytosol across the plasma membrane (34). This in turn leads to activation of downstream Ca²⁺-dependent signaling pathways and nuclear translocation of key transcription factors, which include nuclear factors of activated T-cells (NFAT) and nuclear factor kappa binding (NF-κB) (35). These activities account for T cell responses such as production of various cytokines, as well as proliferation and differentiation into effector cells.

TRPV1 functions as Ca²⁺-permeable channels on the T cell plasma membrane. For instance, a previous study showed that Capsaicin, a special TRPV1 channel agonist, increased Ca²⁺

influx and intracellular Ca²⁺ concentration in activated CD4⁺ T cells, but did not affect resting T cells (36, 37). TRPA1 inhibited the TRPV1 channel activity while deletion of TRPA1 in CD4⁺ T cells increased T-cell receptor-induced Ca²⁺ influx (38). Besides, TRPV1 protein deficiency in CD4⁺ T cells reduced activation of NFAT and NF-κB in response to TCR stimulation and decreased secretion of IL-2 and IFN-γ (31). Moreover, TRPV1 increased Ca²⁺ influx upon stimulation of phytohemagglutinin (PHA) (39). On the contrary, TRPV1-mediated Ca²⁺ influx was not influenced by ionomycin (a Ca²⁺ ionophore) and thapsigargin (a sarcoplasmic reticulum Ca²⁺-ATPase pump inhibitor), which is known to mediate TCR-independent Ca²⁺ activation (31). These studies demonstrated that TRPV1 is a non-store-operated Ca²⁺ channel which modulates TCR-induced Ca²⁺ influx in T cells (31) (Figure 2).

TRPV1 not only promotes T cell activation, but induces T cell death. Previous studies demonstrated that apoptosis of human peripheral T and Jurkat cells were induced in response to exposure to prolonged and high capsaicin concentration (25, 37). Besides, capsaicin-induced apoptosis was associated with intracellular free Ca²⁺ influx (37). In addition, treatment of thymocytes with capsaicin induced autophagy through ROS-regulated AMPK and Atg4C pathways (26). However, the ROS generation was not associated with Ca²⁺ signaling (37).

Temperature Changes Determine the Fate of CD4⁺ T Cells via TRPV1

Similar to free Ca²⁺, temperature changes have been shown to activate the immune system (40). Fever is a physiological response to infections, injuries and inflammation. Fever-range temperatures (1°C~4°C above basal body temperature) are rapidly induced in response to an infection, which in turn

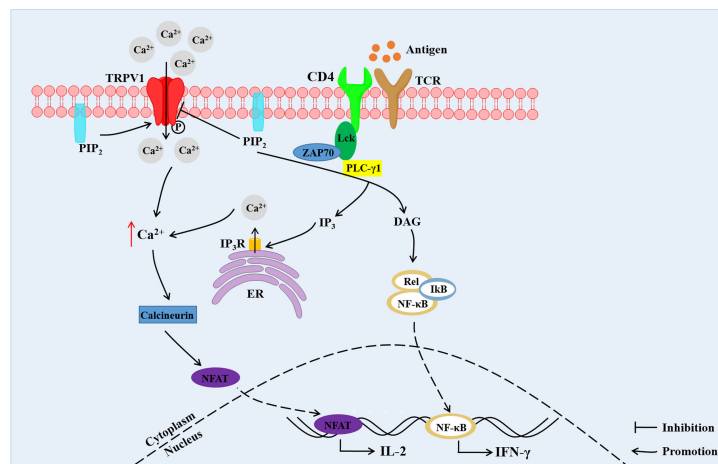


FIGURE 2 | The TCR signals and TRPV1-mediated increase in Ca²⁺ concentration and downstream Ca²⁺-dependent signaling in CD4⁺ T cells. TRPV1 is bound with CD4 and Lck. TRPV1 mediates Ca²⁺ influx, and the tyrosine of TRPV1 is phosphorylated by Lck. PIP₂ located in both leaflets suppresses the activation of TRPV1. Hydrolysis of PIP₂ into DAG and IP₃ by PLC-γ1 leads to relieving of PIP₂-mediated inhibition of TRPV1. Besides, IP₃ binds to IP₃R on ER contributing to the release of Ca²⁺ from intracellular Ca²⁺ store. The increased Ca²⁺ concentration promotes migration of NFAT into the nucleus, inducing the expression of IL-2. DAG promotes the entry of NF-κB into the nucleus, resulting in IFN-γ expression. PIP₂, phosphatidylinositol-4,5-bisphosphate; PLC-γ1, phospholipase C gamma 1; IP₃, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; IP₃R, IP₃ receptor; ER, endoplasmic reticulum; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor kappa binding (33).

boosts protective immune responses, such as immune surveillance. Two studies showed that fever-range temperatures (38~41°C) could promote lymphocytes homing to secondary lymphoid tissues through enhancement of L-selectin and $\alpha 4\beta 7$ integrin-dependent adhesive interactions between circulating lymphocytes and specialized high endothelial venules, thus increasing immune surveillance (41, 42). Another study revealed that fever promoted trafficking of T cells and enhanced immune surveillance during an infection through heat shock protein 90 (HSP90)-induced $\alpha 4$ -integrin activation and increase of $\alpha 4$ -intergrin-mediated T cell adhesion (43). Besides, fever-like whole body hyperthermia (WBH) treatment of mice led to increase in tissue T cells with uropods. Besides, the WBH treatment induced reorganization of protein kinase C (PKC) isozymes and increased PKC activity within T cells (44). In addition, mildly elevated temperature range ($\leq 40^\circ\text{C}$) was shown to strengthen cytotoxic activities of T cells from both adult and cord blood. However, this phenomenon was attenuated on exposure of the T cells to 42°C for 1 hour (45).

On the other hand, temperature changes were shown to affect T cell differentiation. Chen Dong et al. reported that febrile temperature did not influence Th1, Th2 and induced Treg (iTreg) cell differentiation, but selectively and robustly promoted Th17 cell differentiation at 39.5°C. Febrile temperature also elevated Th17 cell cytokine genes (IL-17a, IL-17f and IL-22) and reduced the expression of anti-inflammatory cytokine IL-10 (46). Besides, febrile temperature (38.5°C-39.5°C) fueled the pathogenicity of Th17 cells with a highly pro-inflammatory feature and aggravated experimental allergic encephalomyelitis (EAE) model (46). Mechanistically, febrile-temperature-induced Th17 cell differentiation depended on HSP-70- and HSP-90-related heat shock response and enhanced SUMOylation of SMAD4 transcription factor at its K113 and K159 residues, which facilitated its nuclear localization (46). In sync with the previous findings, Gaublomme and colleagues demonstrated that treatment with anti-fever drugs reduced Th17 cell response *in vivo*, while *in vitro* induced Th17 cells were highly pro-inflammatory in a lung-inflammation model (47) (Figure 3). In addition, naïve CD8⁺ T cells exposed to 39.5°C *in vitro* promoted the rate of synapse formation with APC, which led to differentiation of a greater percentage of CD8⁺ T cells into effector cells (48). This phenomenon was attributed to an increase in membrane fluidity and clustering of GM1⁺CD-microdomains, as well as clustering of TCR β and CD8 co-receptor (48). A recent study showed that fever enhanced production of activated CD8⁺ T cell cytokines and glycolytic metabolism with a limited effect on the expression of CD69, the activation marker (49). Moreover, febrile temperature promoted protective antitumor effects of CD8⁺ T cells *via* mitochondrial translation (49). However, data on how the T cells sense subtle temperature changes remain scant.

TRPV1 is a critical regulator of physiological body temperature and fever, outside the central nervous system (50, 51). TRPV1 could be activated at a temperatures threshold near 43°C (52). A previous study demonstrated that fever sensing by CD4⁺ T cells involve TRPV1 channel during CD4⁺ T cell differentiation (53). In addition, fever-range temperatures significantly enhanced Th2

differentiation and reduced Th1 commitment at moderate fever temperature (39°C) *in vitro via* a TRPV1 channel-mediated Notch-dependent pathway. This was accompanied by upregulation of Th2-relevant transcription factor GATA3, and reduction of the Th1-relevant transcription factor, T-bet (53) (Figure 3). However, both mouse and human naïve CD4⁺ T cells treatment with temperatures between 37°C and 39°C showed no alterations in the activation, proliferation, or cell survival (53). Samivel R et al. revealed suppression of the production of Th2/Th17 cytokines in CD4⁺ T cells and Jurkat T cells upon genetic and pharmacological inhibition of TRPV1 (32).

Together, these data demonstrated that TRPV1 functions as a temperature sensor in CD4⁺ T cells. The temperature changes could regulate CD4⁺ T cell differentiation through TRPV1.

THE FUNCTIONS OF TRPV1 IN T CELL-MEDIATED INFLAMMATORY DISEASES

Inflammation is the main and common pathophysiological feature of pain, visceral inflammation, hypertension and cancer at different stages of occurrence and development (54). Inflammation is characterized by redness, swelling, heat, pain, tissue injury or organ dysfunction (54). Inflammation has been shown to remove tissue injuries and promote restoration during immune responses (54). Recent studies have shown that TRPV1 plays anti-inflammatory roles by attenuating acute and chronic inflammatory processes as well as enhancing homeostasis, thus, attenuating harmful effects of inflammatory responses. Here, we analyzed how TRPV1 modulates T cell-mediated inflammatory responses, which include multiple sclerosis (MS), pulmonary inflammation, inflammatory skin diseases or inflammatory bowel diseases (IBD) as well as osteoarthritis (OA) (Figure 4).

Multiple Sclerosis

Multiple sclerosis (MS) is a complex central nervous system autoimmune disease characterized by autoimmune demyelination and neurodegeneration, which are mediated by Th1 and Th17 cells, macrophages, and immune inflammatory mediators. Previously, TRPV1 mRNA was found to be expressed throughout the central nervous system (CNS), but it was highly expressed in sensory neurons of the dorsal root ganglion (10). The TRPV1⁺ neurovascular complex, referred to as the blood-CNS barrier, promoted invasion of pathogenic lymphocytes (55). However, SA13353, a TRPV1 agonist, reduced the number of cytokines, including TNF- α , IL-1 β , IL-12p40, IL-17, and interferon (IFN)- γ in EAE. In addition, SA13353 attenuated the increase in IL-17-producing cells, demonstrating that SA13353 inhibited the growth of Th17 cells and development of EAE (56). Therefore, TRPV1 channel confers protection by regulating T cells in EAE.

Pulmonary Inflammation

Pulmonary inflammation is caused by infection, physical and chemical factors, immune injury, allergy and drugs, and is

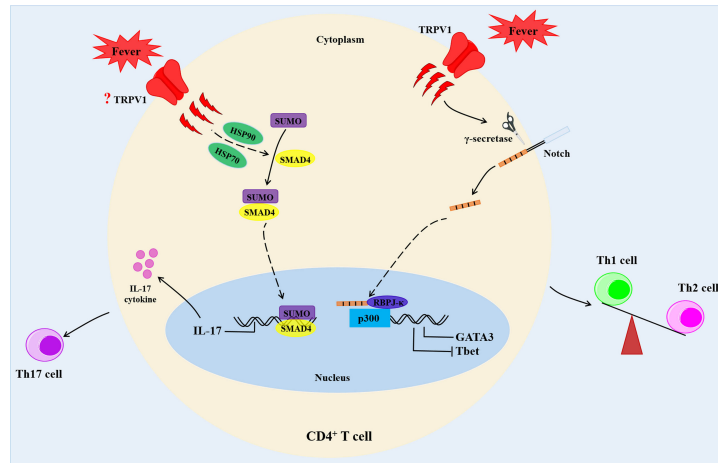


FIGURE 3 | Fever determines the fate of CD4⁺ T cells. Febrile temperature changes enhance Th2 differentiation and reduce Th1 differentiation via a TRPV1-regulated Notch-dependent pathway. In addition, febrile temperature promotes Th17 cell differentiation which depends on HSP-70- and HSP-90-related heat shock response and enhances SUMOylation of SMAD4 transcription factor at its K113 and K159 residues. HSP90, heat shock proteins 90; HSP70, heat shock proteins 70.

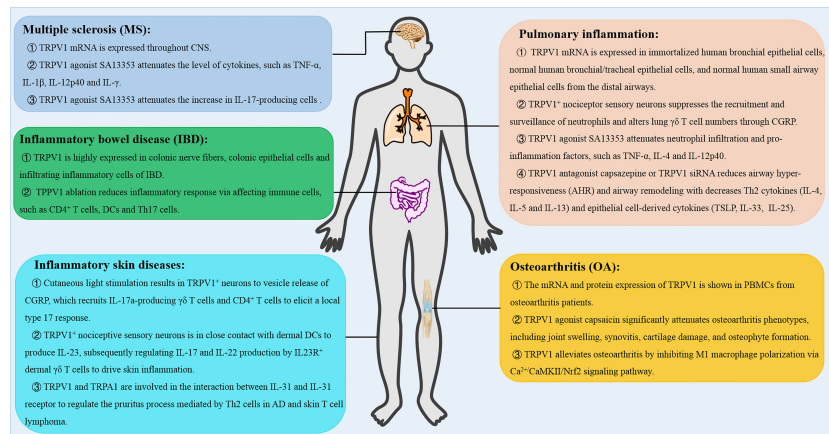


FIGURE 4 | The role of TRPV1 in T cell-mediated inflammatory diseases. TRPV1 regulates the inflammatory responses, such as multiple sclerosis (MS), pulmonary inflammation, inflammatory skin diseases and inflammatory bowel disease (IBD), and osteoarthritis (OA). CNS, central nervous system; AD, atopic dermatitis; CGRP, calcitonin gene-related peptide.

mediated by a variety of inflammatory mediators such as immune cells, chemokines and cytokines. RT-PCR analysis revealed that TRPV1 was expressed in immortalized human bronchial epithelial cells, normal human bronchial/tracheal epithelial cells, and normal human small airway epithelial cells from distal airways (57). In LPS-induced lung injury, SA13353 attenuated neutrophil infiltration and enhanced the TNF- α and CINC-1 levels. In ovalbumin-induced allergic airway inflammation, SA13353 was shown to inhibit leukocyte infiltration and attenuate increase of IL-4 and IL-12p40 (58). Besides, TRPV1⁺ nociceptive sensory neurons suppressed recruitment and surveillance of neutrophils and altered lung $\gamma\delta$ T cells through the release of the neuropeptide calcitonin gene-

related peptide (CGRP) (59). In contrast, treatment with TRPV1 antagonist capsaizepine or TRPV1 siRNA reduced airway hyper-responsiveness (AHR) and airway remodeling with suppressed Th2 cytokines (IL-4, IL-5 and IL-13) and epithelial cell-derived cytokines (TSLP, IL-33, and IL-25) in ovalbumin-induced chronic asthma (60). Therefore, there is a need for further studies to determine the role of TRPV1 in pneumonia.

Inflammatory Skin Diseases

Inflammatory skin diseases refer to skin diseases caused by various internal and external infectious or non-infectious factors, which include psoriasis, atopic dermatitis, allergic contact dermatitis or irritant contact dermatitis. In the absence

of tissue damage or bacterial invasion, cutaneous light stimulation triggered the release of CGRP from TRPV1⁺ neurons, which recruited IL-17a-producing $\gamma\delta$ T cells and CD4⁺ T cells. These cells elicited a local type 17 response that augmented host defense to *C. albicans* and *S. aureus* (61). At the same time, the activated neurons could activate TRPV1⁺ neurons at an adjacent, unstimulated skin through the nerve reflex arc, which provokes the type 17 responses (61). On the other hand, psoriasis is an immune cell-mediated inflammatory skin disease, whose pathogenesis is mediated by IL-23 (62, 63). In imiquimod-induced IL-23-dependent psoriasis-like skin inflammation, TRPV1⁺ nociceptive sensory neurons were shown to interact with dermal dendritic cells to produce IL-23, thus modulating IL-17 and IL-22 production by IL23R⁺ dermal $\gamma\delta$ T cells, which drive skin inflammation (64). Besides, atopic dermatitis (AD) is a common allergic skin disease characterized by skin barrier dysfunction, inflammation and an intense itch (65). IL-31 is an important inflammatory mediator involved in AD, which is closely associated with pruritus (66). Previous data showed that TRPV1 and TRPA1 were involved in the interaction between IL-31 and IL-31 receptor to regulate the pruritus process, which was mediated by Th2 cells in AD and skin T cell lymphoma (67). Based on the important roles played by TRPV1 in skin inflammation and pruritus, the TRPV1 channel is another potential target for skin diseases.

Inflammatory Bowel Disease (IBD)

The occurrence of IBD is driven by chronic inflammation, which is mainly known as Crohn's disease (CD) and ulcerative colitis (UC). Previous data showed that capsaicin, a TRPV1 agonist, attenuated severe combined immunodeficiency (SCID) T-cell transfer colitis, suggesting that the TRPV1 signaling plays a role in capsaicin-mediated attenuation of colitis (68). It was shown that TRPV1 was highly expressed in colonic nerve fibers of IBD patients (69). Luo *et al.* demonstrated high expression of TRPV1 in colonic epithelial cells and infiltrating inflammatory cells of 60 patients with active IBD (30 cases of UC and 30 cases of CD respectively), which was not associated with severity of the disease (70). Moreover, TRPV1 immunoreactive cells were robustly higher in all intestinal layers from active UC patients (71), which suggested that TRPV1 might be involved in immune cells-mediated pathogenesis of IBD. In the T-cell-mediated colitis model, TRPV1 was shown to promote T cell and intestinal inflammatory responses. Inhibition of TRPV1 in T cells by genetic factors or drugs led to reduction of the symptoms of colitis (31, 38). In addition, TRPV1 played an important role in activating mucosal macrophages and maintaining Th17 immune cells in respond to inflammatory stimuli. Overexpression of TRPV1 significantly increased the susceptibility of DSS-induced colitis and promoted DC activation and cytokine production by enhancing the activation of calcineurin/nuclear factor in activated T cell (NFATc2) signaling, and enhancing DC-mediated Th17 cell differentiation upon inflammatory stimulation (72).

In summary, the data indicated that TRPV1 might be a potential therapeutic target in the treatment of mucosal immunity and IBD.

Osteoarthritis (OA)

Osteoarthritis (OA) is a chronic, painful and degenerative disease that affects all joint tissues and results in loss of articular cartilage. Immune cells such as macrophages and T cells in the synovium participate in stimulating and modulating inflammatory responses in OA (73). The TRPV1 mRNA and protein expression were previously detected in PBMCs from OA patients (74). TRPV1 knockout mice showed attenuated chronic phase (>6 weeks) of RA pain (75). In rat OA model, intra-articular injection of capsaicin significantly attenuated OA phenotypes, such as joint swelling, synovitis, cartilage damage, and osteophyte formation (76). Furthermore, TRPV1 alleviated OA by inhibiting M1 macrophage polarization *via* Ca²⁺/CaMKII/Nrf2 signaling pathway (76). These findings demonstrated that TRPV1 regulates various cells in OA.

CONCLUSION AND FUTURE PERSPECTIVES

In this review, we analyze recent data on the expression and functions of TRPV1 in T cells and T cell-mediated inflammatory diseases. The data showed that TRPV1 is a Ca²⁺-permeable channel and mediates TCR-induced Ca²⁺ influx, leading to T cell activation and death as well as differentiation of T cell subsets. However, most of the studies only provided phenotypic observations. Therefore, data on the exact mechanisms underlying the observed phenotypic characteristics is lacking. Besides, whether TRPV1 interacts with other family members or with other channels in T cells remains unclear. In future, scientists should explore interactions between ion channels in T cells, and determine the exact cell-intrinsic roles in T cell development and in different effector T cell subsets.

Furthermore, many studies have demonstrated that TRPV1 can regulate T cell-mediated inflammation and protect the body by regulating production of T cell-related cytokines, such as TNF- α , IL-4 and IL-6. However, due to diverse expression on sensory nerves, immune cells, epithelial cells as well as the consequent activation-induced release of inflammatory mediators, the overall functions of TRPV1 in inflammatory diseases need further evaluation. These data would lay a foundation for future development of new anti-inflammatory drugs targeting TRPV1 in inflammation.

AUTHOR CONTRIBUTIONS

TX and MS wrote the original manuscripts. JK guided on the structure of the manuscript. CZ organized and reviewed the manuscript. CZ and TX provided the funding. All authors contributed to the article and approved the submitted version.

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