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Role of macrophage TRPV4 in inflammation

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Abstract

Transient receptor ion channels have emerged as immensely important channels/receptors in diverse physiological and pathological responses. Of particular interest is the transient receptor potential channel subfamily V member 4 (TRPV4), which is a polymodal, nonselective, calcium-permeant cation channel, and is activated by both endogenous and exogenous stimuli. Both neuronal and nonneuronal cells express functional TRPV4, which is responsive to a variety of biochemical and biomechanical stimuli. Emerging discoveries have advanced our understanding of the role of macrophage TRPV4 in numerous inflammatory diseases. In lung injury, TRPV4 mediates macrophage phagocytosis, secretion of pro-resolution cytokines, and generation of reactive oxygen species. TRPV4 regulates lipid-laden macrophage foam cell formation, the hallmark of atheroinflammatory conditions, in response to matrix stiffness and lipopolysaccharide stimulation. Accumulating data also point to a role of macrophage TRPV4 in the pathogenesis of the foreign body response, a chronic inflammatory condition, through the formation of foreign body giant cells. Deletion of TRPV4 in macrophages suppresses the allergic and nonallergic itch in a mouse model, suggesting a role of TRPV4 in skin disease. Here, we discuss the current understanding of the role of macrophage TRPV4 in various inflammatory conditions.

Introduction

Transient receptor potential vanilloid type 4 (TRPV4) ion channels are nonselective, mechanosensitive, transmembrane Ca^{2+}-permeable cation channels that are ubiquitously expressed in numerous cell types including macrophages [1–14]. TRPV4 channels are activated by a diverse array of biochemical and biomechanical stimuli including mechanical deformation [15–17], osmotic stimuli [18–20], heat [21–24], and by exogenous or endogenous chemical stimuli [6, 25–28]. TRPV4 is associated with numerous physiological functions such as osmolarity sensing in kidneys, sheer-stress sensing in arteries, neurological responses, and the regulation of osteogenesis [1, 29–32]. In mice, absence of TRPV4 is linked to altered pressure/vasodilatory responses, osmosensing, sensory and motor neuropathies, and the development of fibrosis in lung, skin, and cornea [29–34].

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Various biochemical factors including cytokines, chemokines, modified low-density lipoprotein (LDL), and bacterial lipopolysaccharide (LPS) are active in eliciting macrophage-mediated inflammatory responses [10, 35–44]. Emerging reports from our laboratory and others have shown that critical proinflammatory macrophage responses such as phagocytosis, migration, foam cell formation, expression of inflammatory proteins, and proliferation are sensitive to changes in stiffness of their surrounding matrix [10, 36–43]. Therefore, it is important to identify the mechanosensing plasma membrane macrophage receptor/channel by which biomechanical signals are transduced and propagated into cells to drive the generation of inflammatory and other cellular responses. Since TRPV4 is a mechanosensitive channel, and is activated by both biochemical and biomechanical stimuli, it was hypothesized that under certain pathophysiological conditions macrophage TRPV4 may act as a proinflammatory molecule. Intriguingly, emerging data from our laboratory and others have shown that the macrophage TRPV4 is involved in a variety of inflammatory diseases including acute lung injury/acute respiratory disease syndrome, atherosclerosis, foreign body response (FBR), skin disease, and fibrosis [10, 30, 34, 41, 43, 45–50]. Although, the precise mechanism by which TRPV4 orchestrates the pathophysiology of these diseases is not fully understood, these studies suggest that TRPV4 plays a critical role in regulating various inflammatory responses like cytokine production, foam cell formation, giant cell formation, and phagocytosis.

Ca^{2+} is an essential second messenger responsible for modulating an array of cellular responses in numerous cell types, including macrophages. Ca^{2+}-dependent signaling is associated with various macrophage inflammatory responses including atherogenesis, migration, phagocytosis, and foam cell formation [51–56]. The maintenance of macrophage Ca^{2+} homeostasis is in part mediated by ion channels and pumps, and its dysregulation can lead to numerous pathophysiological conditions [57, 58]. Importantly, TRPV4-dependent generation of Ca^{2+} influx has multifarious roles in different cell types including macrophages [1, 2, 5, 6, 11, 14, 29–33, 41, 59]. The current review specifically focuses on the role of macrophage TRPV4 in mediating inflammatory responses.

Pulmonary diseases

Among the present-day lifesaving interventions for acute respiratory distress syndrome, positive pressure mechanical ventilation is one of the most commonly used. However, mechanical ventilation with excessive tidal volumes can in turn contribute to ventilator-induced lung injury(VILI) characterized by a rapid increase in vascular permeability, cytokine release, and inflammatory cell infiltration [60, 61]. Interestingly, it was found that Ca^{2+} entry through TRPV4 initiates the increase in permeability during VILI in isolated mouse lungs [30]. Although earlier studies suggested a possible role of alveolar macrophages in increasing lung permeability in VILI, Hamanaka et al. were the first to identify the mechanical ventilation induced stretch activated TRPV4-dependent lung injury response in alveolar macrophages [46, 62, 63]. Alveolar macrophages from TRPV4 KO mice, after being activated by high volume ventilation, had decreased production of reactive oxygen (ROS) and nitrogen species (RNS), suggesting that TRPV4-dependent generation of ROS and RNS led to the formation of peroxynitrite, which accounted for the increased permeability. Furthermore, in the VILI model, TRPV4 was found to be linked with various

macrophage responses such as spreading, phagocytosis, adhesion, and motility. TRPV4 KO mice failed to develop VILI, but the instillation of WT macrophages into TRPV4 KO mice restored the development of the lung injury, suggesting that mechanical activation of TRPV4 in alveolar macrophages plays a critical role in VILI [46]. Similarly, in a murine high tidal volume ventilation model of lung injury, blocking TRPV4 attenuated both the increase in pulmonary barrier permeability and the increase in proinflammatory cytokine expression by M1 macrophages [64].

Macrophage phagocytosis is a complex phenomenon that has evolved in multicellular organisms as a defense mechanism against foreign particles and pathogens, and as a housekeeping mechanism to clear out apoptotic cells during development and adult life [65–68]. Recently it was shown that LPS-triggered phagocytosis by macrophages of nonopsonized particles in vitro and of opsonized particles in vitro and in vivo was mediated by TRPV4, and that matrix stiffness >25 kPa (mimicking inflamed or fibrotic lungs) augmented this response [41]. Furthermore, this study showed that TRPV4 was essential for LPS-stimulated expression of various cytokines. Taken together, this work suggests a novel role of TRPV4 in macrophage phagocytosis, which could be consequential in physiological functions like resolution of lung inflammation, maintenance of tissue homeostasis, and defense against pulmonary infection and fibrosis. Overall, this study suggests that TRPV4 is sensitized by changes in matrix stiffness as a result of inflamed and/or infected lung, and cooperates with soluble factors including LPS to promote various macrophage responses including phagocytosis.

Tissue injury due to inflammation can lead to the release of an array of proteases such as trypsin, thrombin, and elastases [69, 70]. Protease activating receptor 2 (PAR2) is a G protein coupled receptor that is expressed in alveolar macrophages, endothelial cells, and epithelial cells involved in modulating inflammatory responses, obesity, and metabolism, and can be activated by several proteases [71, 72]. Recently, Rayees et al. identified an anti-inflammatory role of PAR2 in alveolar macrophages by suppression of toll like receptor 4 (TLR4)-induced inflammation [73]. Mechanistically, PAR2-mediated cAMP generation inhibited TRPV4-dependent Ca^{2+} signaling in alveolar macrophages to resolve TLR-elicited inflammation. Depletion of TRPV4 using siRNA or other antagonists in PAR2 null mice blocked Ca^{2+} entry, and also reduced the levels of proinflammatory cytokines and levels of phosphorylation of NFκB and NFAT. Blockade of TRPV4 in PAR2 null mouse alveolar macrophages after LPS challenge promoted the resolution of inflammation and reversed lung injury [73]. Taken together, this study suggests that TRPV4 plays an essential role in mediating inflammation in TLR4-induced responses in alveolar macrophages.

Recent work by Li et al. showed that TRPV4 plays a crucial role in LPS-induced acute lung injury by regulating the calcineurin/NFATc3 signaling pathway [74]. They found that blocking TRPV4 function prevented pneumoedema in LPS-induced lung injury, and resulted in reduced production of proinflammatory molecules TNF-α, IL-6, and ROS. Further, they showed that TRPV4 activated macrophages through Ca^{2+} influx in LPS-induced lung injury. Specifically, they demonstrated that TRPV4 deficiency inhibited LPS-induced calcineurin activation, blocked nuclear translocation of NFATc3 in macrophages, and inhibited release of proinflammatory cytokines. Collectively, these data suggest that TRPV4-mediated Ca^{2+}

influx activates the downstream calcineurin/NFATc3 signaling pathway, which mediates the inflammatory response in acute lung injury.

Atherosclerosis

Atherosclerosis, a leading contributor to mortality and morbidity around the world, is a progressive disease that is characterized by chronic inflammatory responses and fibrofatty lesions in large arteries; atherosclerosis is the principal cause of cerebral and myocardial infarction [75–79]. Injury to vascular endothelium marks the beginning of atherogenesis, which is characterized by trapping of LDL particles in arteries, followed by the expression of numerous inflammatory/adhesion molecules on the surface of endothelial cells [75–79]. Monocytes and T-lymphocytes attach to these molecules, and transmigrate into the arterial intima, where the monocytes differentiate into tissue macrophages, and upregulate expression of scavenger receptors [75–79]. Uptake of oxidized/modified LDL particles by scavenger receptors leads to the formation of macrophage foam cells, a critical atheroinflammatory process in atherosclerosis development [44, 56, 75–80]. The accumulating foam cells along with other cell debris, calcium, lipids, and extracellular matrix form fibro-atheromatous plaques [75–79]. Over the past decade, evidence of the role of inflammation in atherosclerosis, and its associated complications, has continued to grow [75–79, 81]. Earlier studies show that increases in overall oxidative stress attributed to chronic inflammatory conditions can aggravate the process of atherogenesis [75–79].

Ca^{2+} signaling is known to control a diverse array of macrophage functions including phagocytosis, foam cell formation, proliferation, migration, and adhesion [51–58]. Recent studies also report a role of matrix stiffness in the regulation of macrophage function [10, 36–43]. Macrophages are known to express an intricate system of ion channels/pumps that is involved in maintaining cellular calcium homeostasis [57, 58]. Our published data show that TRPV4 is required for oxLDL internalization by macrophages, and for subsequent formation of macrophage foam cells, and that loss of TRPV4 function (either genetic or pharmacological) abrogates foam cell formation [10]. Interestingly, emerging data support a role for a biomechanical factor, e.g., matrix stiffness, in the modulation of numerous proatherogenic macrophage functions, vascular elasticity, and atherogenesis [10, 36–43]. Our group showed that mechanical stimuli like matrix stiffness or scratch-induced macrophage foam cell formation was TRPV4 dependent, and this was particularly important as it mimicked the physiological conditions of atherosclerosis [10]. Future studies will determine how changes in matrix stiffness can lead to activation of mechanosensitive TRPV4 channels in a positive feed-forward manner to promote atheroinflammatory processes in vivo.

Approximately 50% of cardiovascular disease patients lack classic risk factors like hyperlipidemia, smoking, hypertension, and diabetes [76–79, 82]. Both clinical and experimental studies have shown that infection of microbial pathogens including *P. gingivalis* may serve as an additional risk factor in atherosclerosis [83–90]. Interestingly, recent studies suggest an association between periodontal disease and the generation of stiffness in arterial tissues [88, 90]. *P. gingivalis*, a predominant causative agent of periodontal disease, has been previously reported to accelerate proatherogenic processes in

animal models, exerting its effect through various mechanisms including release of LPS, modulating binding/internalization of oxLDL, macrophage foam cell formation, and infiltration of M1 macrophages [83–90]. Published data from our group has recently shown that TRPV4 mechanosensing plays a role in *P. gingivalis*-LPS-triggered augmentation of oxLDL-induced macrophage foam cell formation [43]. Overall our results suggest that TRPV4 integrates LPS and matrix stiffness-induced responses during infection, and elicits Ca^{2+} influx, which mediates macrophage oxLDL uptake and foam cell formation. Although it was found that decreased foam cell formation in TRPV4 deficient macrophages was independent of CD36 (a major scavenger receptor for oxLDL) expression, there was increased co-localization of TRPV4 and CD36 in response to increasing matrix stiffness and LPS. Collectively, these data led us to postulate that increased matrix stiffness in LPS exposed macrophages causes co-localization and crosstalk of TRPV4 and CD36 leading to increased foam cell formation. These findings implicate a possible connection between periodontal infection, TRPV4, and eventual development of atherosclerosis.

Previously, Xu et al. reported an atheroprotective function of TRPV4, in which TRPV4 function in endothelial cells is associated with activation of eNOS and inhibition of monocyte adhesion to endothelial cells [91]. In contrast, deficiency of TRPV4 functions has been linked to numerous atheroinflammatory responses including endothelial dysfunction, reduced macrophage foam cell generation, and vascular diseases [9, 10, 27, 92]. Despite the past findings, an in vivo model supporting these in vitro findings is still missing. ApoE deficient mice have been associated with the development of hypercholesterolemia due to the poor lipoprotein metabolism and clearance, and are an established murine model of atherosclerosis [93, 94]. Thus, for gaining better mechanistic understanding of the link between TRPV4 and atherosclerosis, it is critical to elucidate the in vivo role of this channel utilizing an ApoE/TRPV4 double knockout mouse model, and to determine the responsible molecular mechanisms.

Foreign body response

The FBR is an end stage chronic inflammatory host reaction following implantation of a biomaterial, prosthesis, or medical device into soft tissues; FBR may cause harm to or death of the patient [95–101]. The events leading to the development of the FBR include adsorption of plasma proteins on the biomaterial, activation of complement system, macrophage recruitment and activation, generation of destructive foreign body giant cells (FBGC), and formation of fibrous tissue, which encapsulates the implant [95–101]. Despite the clinical importance of the condition, a thorough molecular understanding of the FBR is still lacking. Macrophages play a central role in development and progression of FBR through their expression of inflammatory proteins, formation of FBGCs, remodeling of the extracellular matrix, and encapsulation of the implant [95–101]. Previous reports by our group and others have shown that various macrophage functions such as phagocytosis, adhesion, and migration are responsive to changes in matrix stiffness, suggesting that biomechanical factors may play a role in the FBR [10, 36–43]. Recently, we reported that genetic ablation of TRPV4, a mechanosensitive channel, protects mice from FBR-related events [49]. TRPV4 deficient mice showed diminished collagen production, reduced macrophage accumulation, and reduced FBGC formation compared with WT mice in a

subcutaneous biomaterial implantation model. Furthermore, we showed that genetic deficiency or pharmacologic inhibition of TRPV4 reduced cytokine-induced FBGC formation, which was restored by lentivirus-mediated TRPV4 reintroduction. Altogether, these results suggest an important, previously unsuspected role for TRPV4 in FBR. Delineation of the underlying TRPV4 activation and subsequent mechanism may identify attractive targets for future therapeutic intervention for FBR.

Fibrosis and chronic itch

The role of TRPV4 in fibrosis and chronic itch is an emerging area of research, and many groups including ours are interested in determining how this mechanosensitive Ca^{2+}-permeant channel regulates various lung and skin related pathologies. Fibrosis or scar formation cause chronic pathological conditions in lung, heart, kidney, skin, and liver, which are characterized by accumulation of myofibroblasts, epithelial-mesenchymal transition (EMT), and secretion of extracellular matrix proteins [102–105]. Tissue injury and exacerbated/uncontrolled myofibroblast differentiation are critical steps in the pathogenesis of fibrosis [102–105]. Various immune cells, specifically inflammatory monocytes and tissue-resident macrophages are key drivers of tissue regeneration and fibrosis [106]. Following tissue damage, monocytes/macrophages undergo phenotypic and functional transitions enabling their participation in various phases of tissue repair [106]. However, aberrant macrophage responses can lead to uncontrolled tissue repair due to sustained production of inflammatory mediators, growth factors, lack of M2 macrophages, excessive EMT, exacerbated myofibroblast generation, and aberrant activity of stem or tissue progenitor cells [106]. Previously, we reported that TRPV4 is associated with skin and lung fibrosis [11, 13, 14]. TRPV4 regulates both biochemical (Transforming growth factor β1)- and biomechanical (matrix stiffness) stimulus-induced lung and dermal myofibroblast differentiation, which is associated with fibrosis development in scleroderma, and contributes to the development of in vivo pulmonary and skin fibrosis in murine models [11, 14, 33]. We also showed that TRPV4 plays an important role in EMT in both human and murine primary keratinocytes [107]. However, the specific role of macrophage TRPV4 in fibrosis has not been determined. Development of cell-type specific animal models might shed more light into this relatively less explored area of research.

Chronic itch, a symptom of numerous skin disorders, is still poorly understood at the molecular level, and treatments are largely ineffective [108, 109]. Previous studies have identified hypotonicity and metabolites of the mevalonate pathway as activators of TRPV4-mediated nociception [110, 111]. However, Luo et al. in a recently published report, showed that the osmosensitive TRPV4 channels are selectively expressed in dermal macrophages and keratinocytes, and deletion of TRPV4 in macrophages and keratinocytes suppressed allergic and nonallergic itch in mice [109]. Skin biopsy samples from chronic idiopathic pruritus patients also had significantly higher expression of TRPV4 compared with healthy controls. Furthermore, their studies show that 5-hydroxytryptamine signaling is a critical downstream component of TRPV4-mediated allergic and nonallergic itch

Okada et al. used a corneal alkali burn wound healing model to determine the role of TRPV4 in corneal fibrosis [34]. They found higher TRPV4 expression in stromal cells after

activation by alkali burn compared with the WT. They found that stromal opacification, due to development of fibrosis, was markedly reduced in TRPV4 KO mice. Immunohistochemistry data showed that TRPV4 KO mice failed to exhibit the expected fibrosis-associated increase in numbers of polymorphonuclear leukocytes and accumulation of macrophages. Furthermore, the data showed that macrophage release of interleukin-6 was reduced. Reciprocal bone marrow transplantation studies between WT and TRPV4 KO chimeric mouse models showed that reduced fibrosis and inflammation in TRPV4 KO mice were attributable in part to the loss of TRPV4 expression in macrophages. Altogether, these results suggest that alkali-induced corneal fibrosis and inflammation were, in part, dependent on macrophage TRPV4.

Conclusions

Inflammation is a vital part of the immunological response to injury and infection. However, it can also lead to tissue injury or destruction if unchecked. The role of TRPV4 in inflammatory diseases is being studied by several groups. In the setting of pulmonary diseases, macrophage TRPV4 has been seen to modulate both inflammatory and anti-inflammatory functions through its role in phagocytosis, release of cytokines, and regulation of signaling processes. TRPV4 was shown to be a novel regulator of matrix stiffness and LPS-induced oxLDL-mediated macrophage foam cell formation, a critical atheroinflammatory process in atherosclerosis. Emerging evidence also suggests a role of macrophage TRPV4 in FBR, fibrosis, and chronic allergic and nonallergic itch. Elucidation of the precise role and mechanism of macrophage TRPV4 in inflammatory conditions will be important for developing targeted therapeutics for the resolution of inflammatory diseases.

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