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Role of Transient Receptor Potential Channels in Heart Transplantation: A Potential Novel Therapeutic Target for Cardiac Allograft Vasculopathy

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Heart transplantation has evolved as the criterion standard therapy for end-stage heart failure, but its efficacy is limited by the development of cardiac allograft vasculopathy (CAV), a unique and rapidly progressive form of atherosclerosis in heart transplant recipients. Here, we briefly review the key processes in the development of CAV during heart transplantation and highlight the roles of transient receptor potential (TRP) channels in these processes during heart transplantation. Understanding the roles of TRP channels in contributing to the key procedures for the development of CAV during heart transplantation could provide basic scientific knowledge for the development of new preventive and therapeutic approaches to manage patients with CAV after heart transplantation.

MeSH Keywords: **Endothelial Cells • Heart Transplantation • Muscle, Smooth, Vascular • Transient Receptor Potential Channels**

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Background

In modern society, due to smoking, poor diet, physical inactivity, high blood cholesterol, and many other factors, more and more people suffer from cardiovascular system diseases. As a common outcome of many different kinds of cardiovascular system diseases, the number of patients with heart failure is increasing [1]. Advanced heart failure is associated with increasing morbidity and mortality, requiring recurrent hospitalization and dramatic decrease in quality of life. Although mechanical circulatory support technology is improving, it is inevitably accompanied by many severe complications, including stroke, bleeding, and infection. Thus, heart transplantation with median survival exceeding 10 years is still recognized as the criterion standard therapy for end-stage heart failure [2–4]. Advances in the fields of organ preservation, immunosuppression, infection prophylaxis, and surgical techniques have transformed heart transplantation from an experimental intervention into a routine treatment [5]. The overall survival rate of heart transplant patients has improved significantly over the last 3 decades. However, cardiac allograft vasculopathy (CAV), a unique and rapidly progressive form of atherosclerosis in heart transplant recipients, continues to be a major cause of mortality during the first year after a heart transplant [6]. Although the pathogenesis of CAV is not been completely understood, many studies show that the development of a CAV lesion is preceded by vascular inflammation, endothelial dysfunction, and vascular smooth muscle cell proliferation [6–10]. Based on these studies, we suggest that transient receptor potential (TRP) channels as cellular sensors for various internal and external stimuli play crucial roles in the pathophysiological processes of vascular inflammation, endothelial dysfunction, and smooth muscle cell proliferation during heart transplantation and may become an effective therapeutic intervention target to attenuate the progression of CAV.

Pathogenesis of CAV

During heart transplantation, recipients with classical risk factors such as hyperlipidemia, hypertension, diabetes, or metabolic syndrome, and transplant-associated risk factors such as ischemia-reperfusion injury, human leukocyte antigen (HLA) mismatching, preservation damage, and cytomegalovirus (CMV) infection are more likely to trigger severe vascular inflammation, endothelial injury and dysfunction, and vascular smooth muscle cell proliferation through multifactorial and complex processes than recipients who do not have these risk factors [6,7,11]. It is still difficult to define all the risk factors associated with the development of CAV and to elucidate the whole pathogenesis; however, vascular inflammation, endothelium injury and dysfunction, and vascular smooth muscle cell proliferation are widely known as the 3 most important processes in the development of CAV [6–10] (Figure 1). All of these 3 key pathophysiological processes are associated with specific cell cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) in varying degrees. TRP channels, as cellular sensors for various internal and external stimuli and relative permeability to Ca^{2+}, may be the key modulators in the development of CAV.

TRP Channels

TRP channels constitute a large superfamily of cation channel-forming proteins. To date, 28 different mammalian TRP channel members subdivided into 7 subfamilies (TRPC, TRPV, TRPM, TRPP, TRPN, TRPML, and TRPA) have been identified. All TRP channels contain 6 transmembrane-spanning regions with a pore-forming reentrant loop between the fifth (S5) and the sixth (S6). Both the carboxyl(C)- and amino(N)-termini are intracellular. In terms of ion selectivity, all functional TRP

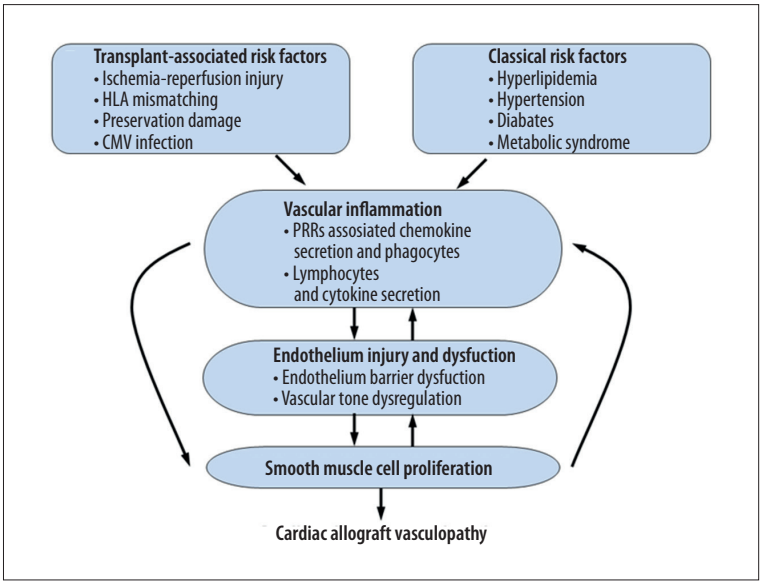

Figure 1. Pathogenesis of CAV. Recipients with transplant-associated risk factors and classical risk factors have severe vascular inflammation, endothelial injury and dysfunction, and this stimulates vascular smooth muscle cell proliferation through a multifactorial and complex process. Then, vascular inflammation and endothelium dysfunction, as well as vascular smooth muscle cell proliferation and migration, in these 3 key processes will ultimately cause coronary diffused concentric intimal thickening and CAV.

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channels are cation permeable. Relative permeability to Ca^{2+} compared to Na^{+} ranges from >100 for TRPV5 and TRPV6 to ~0 for TRPM4 and TRPM5 [12,13]. As for gating mechanisms, there is an interesting variation within the TRP superfamily, which includes temperature-, light-, capsaicin-, shear stress-, osmolarity-, extracellular pH-, voltage-, and ligand-gated channels. We can regard TRP channels as cellular sensors for various internal and external stimuli [13,14]. Consequently, dysfunction of TRP channels may participate in a variety of human diseases.

TRP Channel and Vascular Inflammation

Heart transplantation, with the stimulation of endogenous and exogenous "antigen", inevitably activates innate and adaptive immune systems which then form an inflammation milieu favorable to endothelium injury [15,16]. TRP channels, as cellular sensors for various internal and external stimuli, are widely distributed in various immunocytes and play important roles in the process of vascular inflammation.

TRP channels and innate immune-associated inflammation

The physical processes of isolating, removing, reimplanting, and reperfusing organs inevitably result in stress responses and local tissue damage, subsequently releasing a series of damage-associated molecular patterns (DAMPS) such as heat shock protein 70 (Hsp70), reactive oxygen species (ROS), and high-mobility group box 1 (HMGB1) [17–19]. Some specific cells that express pathogen-associated pattern recognition receptors (PRRs), such as endothelial cells, dendritic cells, and macro-phagocytes, can sense DAMPS and initiate an inflammatory response by rapidly releasing inflammatory mediators such as TNF-α, IL-1, IL-6, and chemoattractant cytokines, attracting neutrophils, monocytes, and other immune cells into the graft [20,21]. In this process, Toll-like receptors (TLRs) and NOD-like receptors (NLRs) are 2 kinds of PRRs that can provide immediate responses against ischemia-reperfusion or pathogenic invasion. Ao et al. demonstrated that ischemia-reperfusion leads to the release of Hsp70 from the heart and then leads to the TLR4 dependent inflammatory response [22]. An increasing number of studies have indicated that the TLR-mediated immune response is associated with TRP channel-dependent Ca^{2+} signaling [23]. Tauseef et al. identified a function of TRPC6 in endothelial cells, showing that TRPC6-dependent Ca^{2+} signaling intersects with the TLR4 signaling pathway and hence contributes to lung inflammation [24]. In addition to TRPC6, TRPV1 and -V2 have also been observed to participate in the TLR4 activation, as well as TNF-α and IL-6 expression [25,26]. ROS plays a central role in NLRP3 inflammasome activation, but how ROS signaling contributes to the assembly of NLRP3 inflammasome remains elusive. Zhong et al. identified the liposome as a novel activator of the NLRP3 inflammasome and further demonstrated that stimulation with liposomes/crystals induces ROS-dependent calcium influx via the TRPM2 channel. Macrophages deficient in TRPM2 drastically impair NLRP3 inflammasome activation and IL-1β secretion [27]. Similarly, Yamamoto et al. implicated TRPM2-mediated calcium influx in ROS-induced CXCL2 secretion in monocytes [28]. Based on these findings, further studies are needed to elucidate the relationship between TRP channels and NLRP3. On the other hand, Lindemann et al. found that TRPC1 is involved in fMLP-mediated migration and chemotaxis of murine neutrophils. The loss of TRPC1 reduces neutrophil migration, transmigration, and chemotaxis [29]. Collectively, these studies indicate that TRP channels are a key bridge that links DAMPS to PRRs and may be an effective target for the treatment of DAMPS and PRRs-associated inflammatory disorder.

TRP channels and adaptive immune-associated inflammation

Besides the innate immune system, TRP channels also participate in B and T lymphocyte activation and cytokine secretion in response to various foreign antigens. As for B lymphocyte, Mori et al. showed that genetic disruption of TRPC1 significantly attenuates both Ca^{2+} release-activated Ca^{2+} currents and Ca^{2+} release from the endoplasmic reticulum in DT40 B lymphocytes. Consequently, B cell antigen receptors-mediated Ca^{2+} oscillations and nuclear factor for T cells activation (NF-AT) were reduced in TRPC1-deficient lymphocytes [30,31]. In addition to TRPC1, the $[Ca^{2+}]_i$ elevation of B lymphocytes can also occur through TRPC3 and TRPV4-like channels activated separately by pathogen-derived CpG DNA, fluid shear, and osmotic forces [32]. Therefore, the normal function of B lymphocytes depends on the expression of particular TRP channels. For T lymphocytes, Wenning found that TRPC3 mRNA is strongly upregulated in human primary CD4+ T cells following TCR stimulation, and siRNA-mediated knockdown of TRPC3 led to a decrease in Ca^{2+} influx and proliferation [33]. Furthermore, Philipp et al. found that the TRPC3 channels are important to the T cell receptor (TCR)- dependent Ca^{2+} entry pathway. Subsequently, the elevated calcium concentration is necessary for antigen-dependent T cell activation and T cell-dependent immune responses [30,34]. The paramount importance of TRPC channels in the control of lymphocyte clonal expansion and cytokine secretion makes it an excellent target for novel anti-inflammatory drug therapies. Majhi et al. also confirmed the critical role of TRPV1 in mediating TCR-induced Ca^{2+} influx and cytokine production in mouse and human primary T cells by using I-RTX (a specific TRPV1 antagonist) [35]. Controlling inflammation through TRP channels may be the crucial missing piece in the puzzle of preventing CAV. In addition, Song et al. reported that a TRPML-dependent process is required for normal regulation of the specialized lysosome compartment of vertebrate B lymphocytes, the regulated transformation of which has been implicated in B cell antigen presentation [36]. TRPML

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channels may become another target to break the bridge between the innate and adaptive immune systems.

TRP Channels and Endothelium Injury and Dysfunction

The endothelium, which lines the endothelial layer of vascular trees, not only acts as a semi-permeable dynamic barrier, but is also actively involved in a variety of physiological and pathophysiological processes, such as the regulation of vascular tone, coagulation, fibrinolysis, and vascular inflammatory reactions [37,38]. TRP channels, as cellular sensors for various internal and external stimuli, participate in inflammation to mediate endothelium injury and also have crucial roles in endothelial barrier dysfunction and vascular tone regulation [39].

TRP channels and endothelial barrier dysfunction

The permeability of the endothelial barrier is balanced by the contraction force of the endothelial cells and the adhesive force that holds the cells in a flattened state. Besides direct injury to the endothelium, inflammatory cytokines and growth factors act on the endothelial barrier to initiate a cascade of events that result in an increase in the contraction force or decrease in the adhesive force, which enlarge the inter-endothelial gap. This may lead to the exposure of underlying smooth muscle cells and extracellular matrix (ECM) to blood components and potential for thrombosis and leukocyte infiltration [40]. One of the early events that participates in this signaling cascade is the rise of endothelial $[Ca^{2+}]_i$. Several TRP channels, including TRPC1, -C4, and -C6, are reported to be involved in this process [39]. The increasing expression of TRPC1, either by stimulating endothelial cells with TNF-α or by TRPC1-cDNA transfection, results in an excessive Ca^{2+} influx, which exaggerates the thrombin-induced increase in actin-stress fiber formation and leads to endothelial barrier dysfunction [41,42]. Like TRPC1, deletion of the TRPC4 gene can also reduce the thrombin-induced increase in endothelial permeability. Evidence also shows that TRPC1 and -C4 actually form heteromultimeric channels as the molecular basis of a capacitative Ca^{2+} channel in endothelium [43,44]. Pocock et al. found the vascular endothelial growth factor (VEGF)-induced increases in vascular permeability can be mimicked by flufenamic acid, which is the activator of TRPC6 [45,46]. The data suggest that TRPC6 may have a role in VEGF-mediated vascular barrier dysfunction. Based on these results, TRPC channels may become an excellent target for preventing endothelial barrier dysfunction.

TRP channels and vascular tone regulation and dysregulation

The endothelium plays a critical role in sensing changes in blood-borne signals and hemodynamic forces and responds to these stimuli by releasing vasoactive substances that regulate vascular tone. During heart transplantation, the injured coronary endothelium can neither effectively sense changes in hemodynamic forces and blood-borne signals nor respond to these stimuli by releasing specific vasoactive substances. The vascular homeostasis balance is disrupted, and the consequent effects on the vasculature are abnormal vasoconstriction, leukocyte adherence, platelet activation, vascular inflammation, and the development of CAV [8,47]. TRP channels, as cellular sensors, not only participate in sensing vascular signals, but also have crucial roles in releasing vasoactive substances. Nitric oxide (NO), a key mediator of vascular tone regulation and vascular SMC proliferation, is often depleted in endothelium injury [47]. However, it has been found that a rise in endothelial $[Ca^{2+}]_i$ can stimulate endothelial NO synthase. Studies have demonstrated some TRP channels, such as TRPC, TRPV, TRPP, and TRPM, can sense some blood-borne signals or hemodynamic forces to mediated endothelial $[Ca^{2+}]_i$ increases, then stimulate endothelial NO synthase (eNOS) and release. For example, vascular activators such as acetylcholine (Ach) can activate TRPC4 expression on vascular endothelial cells to regulate the vascular tone. In mice that lack TRPC4, agonist-induced Ca^{2+} entry in aortic endothelial cells is dramatically diminished, and as a consequence, endothelium-dependent vascular relaxation in response to vasoactive agent acetylcholine is also impaired [48]. TRPC5 and -C6 have similar function as TRPC4, but at this point the vascular activators are ATP and bradykinin [49,50]. TRPV1 and -V4 are 2 other channels associated with vascular tone. TRPV1 channel expression in rat vascular endothelium can be activated by capsaicin and significantly increase NO secretion. For TRPV4, it has been shown that arachidonic acid can activate this channel expressed in rat coronary endothelium, causing endothelium-dependent vascular relaxation [51]. Additionally, TRPV4, TRPP1-P2 complex, and TRPM7 channels act as flow-sensitive Ca^{2+} channels. They are activated by shear stress change and mediate endothelial $[Ca^{2+}]_i$ increase, contributing to stimulation of endothelial NO synthase to regulate the vascular tone [52–56]. In addition to the mechanisms mentioned above, studies found that NO itself can modulate TRP channels, including TRPV1, -V3, -V4, -C5, -C3, -C6, and -M4 through feedback mechanisms to preserve homeostasis [39,57]. Besides the activation of eNOS, TRP channels can also alter plasma membrane potential and have an endothelium-derived hyperpolarizing factor (EDHF)-dependent dilation function. The increase of endothelial $[Ca^{2+}]_i$ opens endothelial small-conductance K_{Ca} (SK_{Ca}) and intermediate-conductance K_{Ca} (IK_{Ca}) channels, which results in K^+ efflux and endothelium hyperpolarization [58, 59]. This hyperpolarization is then directly transmitted to smooth muscle cells (SMCs) through corresponding gap junctions and ultimately causes vascular SMC relaxation [59].

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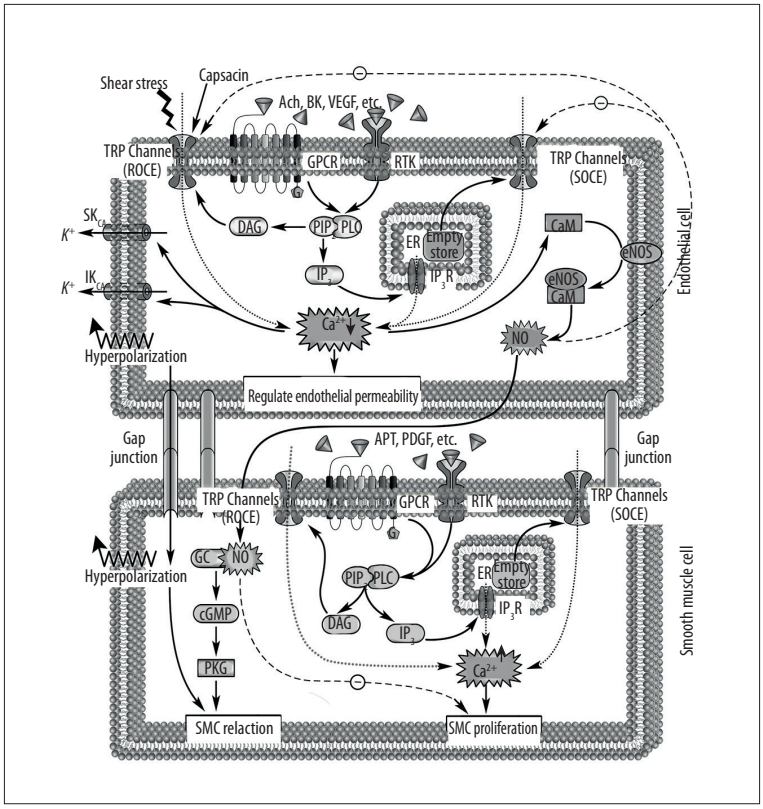

Figure 2. TRP channels in vascular endothelium dysfunction and smooth muscle cell proliferation. Stimulation of the vascular endothelial PLC system, mainly by G protein-coupled receptors (GPCR) and receptor protein tyrosine kinases (RTK), by Ach, bradykinin, VEGF, and other ligands are capable of generating IP_3 and DAG. On the one hand, IP_3 can deplete the endothelium reticulum (ER) Ca^{2+} store. This store depletion process activates signaling molecules, which mediate Ca^{2+} entry through some TRP channels (such as TRPC1 and -C4) acting as a store-operated Ca^{2+} entry (SOCE). On the other hand, DAG can directly stimulate some TRP channels (such as TRPC6), which act as a receptor-operated Ca^{2+} entry (ROCE). In addition to the above mechanisms, external stimuli such as capsaicin and shear stress can directly act on some specific TRP channels (such as TRPV1, -V4, TRPP1-P2 complex, and TRPM7) to induce Ca^{2+} influx. The increased Ca^{2+} concentration has 3 main functions: Firstly, the elevation of $[Ca^{2+}]_i$ can open endothelial small-conductance K_{Ca} (SK_{Ca}) and intermediate-conductance K_{Ca} (IK_{Ca}) channels, resulting in K^+ efflux and endothelium hyperpolarization, which be directly transmitted to SMC through corresponding gap junctions and ultimately causes vascular SMC relaxation. Secondly, the elevation of $[Ca^{2+}]_i$ activates the Ca^{2+} -dependent protein kinase C (PKC) isoform, PKC-α, which mediates cytoskeletal reorganization and disassembly of vascular endothelial cadherin at the adherens junctions, and ultimately regulates endothelium permeability. Finally, the elevation of $[Ca^{2+}]_i$ forms Ca^{2+}-CaM (calmodulin), which then activates eNOS and leads to the amplified production of NO. NO itself can modulate some TRP channels through feedback mechanisms to preserve homeostasis; it diffuses out of endothelium into adjacent SMCs and stimulates guanylate cyclase (GC), which leads to the activation of PKG and SMC relaxation to regulate vascular tone, and endothelium-derived NO can also inhibit vascular SMC proliferation. In SMCs, stimulation of the vascular PLC system by platelet-derived growth factor (PDGF) and other ligands is capable of generating IP_3 and DAG, and IP_3 acts on TRPC1, -C3, -C4, -C5, and -C6 to increase $[Ca^{2+}]_i$ through a mechanism similar to that found in the endothelium. DAG can also directly stimulate TRPC3, -C6, and -C7, which acts as a receptor-operated Ca^{2+} entry (ROCE) in this process. The elevated $[Ca^{2+}]_i$ of SMCs then initiates the proliferation response of SMCs by stimulating various transcription factors.

TRP Channels and Smooth Muscle Cell Proliferation

The SMC is not only a contractile cell, but also acts as a multi-function cell with other important roles such as proliferation, migration, and production of cytokines, participating in the pathogenesis of various disease [60]. During heart transplantation, recipients with risk events will inevitably have stimulation of vascular SMC proliferation and migration from different points, which ultimately results in vascular remodeling. These present as the most fundamental and perturbed feature of CAV [61]. Studies have found that the proliferation and migration of SMCs are dependent on a key event: the increase of intracellular calcium contraction. Similar to endothelium, calcium entry

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from the extracellular space is a major step in the elevation of $[Ca^{2+}]_i$ in SMCs and involves a variety of plasmalemmal calcium channels, including the TRPC channel, which operates as specific Ca^{2+} pathways responsive to stimuli, including growth factors, circulating agonists, and Ca^{2+} store depletion [60,62–64]. Some growth factors and specific ligands like platelet-derived growth factor (PDGF), epidermal growth factor (EGF), endothelin-1 (ET-1), and serotonin (5-HT) are capable of activating the pulmonary vascular phospholipase C (PLC) system and generating Ins(1,4,5)P_3 and DAG [63,65,66]. Ins(1,4,5)P_3 releases Ca^{2+} from the endoplasmic reticulum (ER) through the Ins(1,4,5)P_3 receptor (InsP_3R1). Emptying of this store activates TRPC1, -C3, -C4, -C5, and -C6, which act as store-operated channels (SOCs). PLC can also directly activate receptor-operated channels (ROCs), including TRPC3, -C6, and -C7 via the production of DAG to enhance cellular Ca^{2+} elevation [62,64] (Figure 2). In addition to the mechanisms mentioned above, some growth factors and specific ligands also increase intracellular calcium contraction by enhancing the transcription of some TRP channels. Incubation of human pulmonary artery SMCs with ATP will induce phosphorylation of the cyclic AMP response element-binding protein (CREB), a critical transcription factor involved in the increased transcription of TRPC4 and enhanced TRPC4 expression, store-operated Ca^{2+} entry (SOCE), and cell proliferation [67]. Furthermore, PDGF stimulates signal transducer and activator of transcription 3 (STAT3) through phosphorylation, leading to the up-regulation of c-Jun, which activates the transcription of TRPC6, resulting in enhanced SOCE and vascular SMC proliferation [68,69]. In spite of these results, there is still no evidence to demonstrate whether or not TRPC channels participate in the development of CAV during heart transplantation, and further studies are needed. Regulating the expression of TRPC channels may become a very effective therapeutic intervention to attenuate vascular SMC proliferation of CAV.

Conclusions

It is becoming clear that vascular inflammation, and endothelium injury and dysfunction, as well as vascular smooth muscle cell proliferation, are the 3 most important pathophysiological processes in the development of CAV. In this review, we summarize recent studies that demonstrate the functional expression and critical role of TRP channels in these pathophysiological processes. TRPC6, TRPV1, and -V2 have been observed to participate in TLR4 activation and TNF-α, IL-6 expression. Similarly, TRPM2-mediated calcium influx participates in ROS-induced CXCL2 secretion in monocytes. Besides the innate immune system, TRPC1, TRPC3, and TRPV4-like channels also participate in the activation, and T cell activation of B lymphocytes, and TRPC3, TRPV1 channel-mediated elevated calcium concentration is necessary for antigen-dependent T cell activation and cytokine production in human primary T cells. These studies indicate that TRP channels may be effective targets for immunosuppression of the innate and adaptive immune systems, as well as vascular inflammation. In addition to these mechanisms, TRPC1, -C4, and -C6 participate in permeability regulation of the endothelial barrier and may become targets for preventing endothelial barrier dysfunction. Furthermore, members of TRPC, TRPV, TRPP, and TRPM subfamilies can also sense certain blood-borne signals or hemodynamic forces to mediated endothelial $[Ca^{2+}]_i$ increases, then stimulate endothelial NO synthase and release NO to regulate vascular tone. PDGF results in enhanced SOCE and vascular SMC proliferation by stimulating signal transducer and activating the transcription of TRPC6. The TRPC4 channel can also participate in ATP-induced human artery proliferation of SMCs. Thus, regulating the expression of TRPC channels may become a therapeutic intervention to attenuate the vascular SMC proliferation of CAV.

We propose that the regulation of the expression of the associated TRP channels may effectively limit the pathophysiological processes of vascular inflammation, endothelial injury and dysfunction, and vascular smooth muscle cell proliferation during heart transplantation, and we believe that TRP channels may become an effective therapeutic intervention target to attenuate the progression of CAV.

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Conflict of interest

The authors declare that they have no conflict of interest.

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