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Review

TRP channels in endothelial function and dysfunction

Hiu-Yee Kwan, Yu Huang, Xiaoqiang Yao *

Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China
Department of Physiology, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China

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Abstract

Endothelial cells produce various factors that regulate vascular tone, vascular permeability, angiogenesis, and inflammatory responses. The dysfunction of endothelial cells is believed to be the major culprit in various cardiovascular diseases, including hypertension, atherosclerosis, heart and renal failure, coronary syndrome, thrombosis, and diabetes. Endothelial cells express multiple transient receptor potential (TRP) channel isoforms, the activity of which serves to modulate cytosolic Ca^{2+} levels ($[Ca^{2+}]_i$) and regulate membrane potential, both of which affect various physiological processes. The malfunction and dysregulation of TRP channels is associated with endothelial dysfunction, which is reflected by decreased nitric oxide (NO) bioavailability, inappropriate regulation of vascular smooth muscle tonicity, endothelial barrier dysfunction, increased oxidative damage, impaired anti-thrombogenic properties, and perturbed angiogenic competence. Evidence suggests that dysregulation of TRPC4 and -C1 results in vascular endothelial barrier dysfunction; malfunction of TRPP1 and -P2 impairs endothelial NO synthase; the reduced expression or activity of TRPC4 and -V1 impairs agonist-induced vascular relaxation; the decreased activity of TRPV4 reduces flow-induced vascular responses; and the activity of TRPC3 and -C4 is associated with oxidative stress-induced endothelial damage. In this review, we present a comprehensive summary of the literature on the role of TRP channels in endothelial cells, with an emphasis on endothelial dysfunction.

1. Endothelial function and dysfunction

The endothelium, which lines the blood vessels of vascular trees, is not an inert barrier but rather a highly active cell layer that is involved in a variety of physiological and pathophysiological processes. Endothelial cells participate in the regulation of vascular tone, coagulation and fibribolysis, vascular inflammatory reactions, and blood vessel formation [1]. As with any other organ, the endothelium is subject to dysfunction and failure. Endothelial dysfunction can be broadly defined as disturbance of endothelial cell function that is induced by diverse intrinsic and extrinsic factors. Such dysfunction is reflected by decreased nitric oxide (NO) bioavailability, inappropriate regulation of vascular smooth muscle tonicity, impaired antithrombogenic properties, and perturbed angiogenic competence [2–4]. These changes are the genesis of various cardiovascular pathologies, such as hypertension and atherosclerosis [2–4]. In humans, endothelial dysfunction can be assessed biochemically by dosing different markers in the blood, including adhesion molecules, cytokines, prostanoids, and nitrites and nitrates [2]. Endothelial dysfunction can also be assessed functionally through the measurement of arterial stiffness, intima-to-media thickness ratio, endothelium-dependent dilation in the arteries, or changes in blood flow in forearm, coronary, or peripheral circulation in response to agonists [2].

2. TRPs in endothelial cells

The TRP channels are a group of cation channels that function as cellular sensors for various internal and external stimuli [5]. Among the 28 unique mammalian TRP channel isoforms that have been identified, at least 19 (all of the TRPC; TRPV1, -V2, and -V4; all of the TRPM except -M5; and TRPP1 and -P2) are expressed in vascular endothelial cells [6]. These channels regulate two vital parameters in endothelial cells: $[Ca^{2+}]_i$ and cell membrane potential. In terms of the first parameter, all TRP channels, except for TRPM4 and -M5, are Ca^{2+}-permeable, and

* Corresponding author. Department of Physiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China. Tel.: +852 26096877; fax: +852 26035022.
E-mail address: yao2068@cuhk.edu.hk (X. Yao).

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Table 1
TRP channels in vascular cells: activation mechanisms, its linkage to vascular function and dysfunction

Channel	Chromosome	Activation mechanisms	Functions and diseases
TRPC1	3q22–3q24	Thrombin [14,15], bFGF [26] store depletion [14,42], stretch [57]	Endothelial barrier dysfunction [14,15,16], intimal thickening and atherosclerosis [70], angiogenesis [7,26,27,28]
TRPC3	4q27	Oxidant [19,20], DAG [7], VEGF [27]	Oxidative stress-induced endothelial damage [19,20], essential hypertension [66], idiopathic pulmonary arterial hypertension [67], Angiogenesis [7,27,28]
TRPC4	13q13.1–q13.2	Oxidant [20], thrombin [16,17] ATP [17], acetylcholine [17,21,13] store depletion [16,17,18,21,42]	Oxidative stress-induced endothelial damage [19,20], endothelial barrier dysfunction [16,17,18], endothelial-dependent vascular relaxation [21]
TRPC5	Xq23	ATP [33], S-nitrosylation [33]	Heart failure [68], essential hypertension [66]
TRPC6	11q21–22	Bradykinin [32], VEGF [7,27] DAG [7], stretch [9,58,61]	Endothelial barrier dysfunction [7], angiogenesis [7,27,28], idiopathic pulmonary arterial hypertension [67]
TRPM2	21q22.3	ADP-ribose, NAD, H_2O_2 [37,39,41]	Oxidative stress-induced cell death? [37,39,41]
TRPM4	19q13.33	NO inactivated [35], PIP_2, stretch [60]	Decreased NO production? [35]
TRPM7	15q21	Oxidant [40], shear stress [56], PIP_2	Angiogenesis? [6] Oxidative stress-induced cell death? [40]
TRPV1	17p13.3]	Endocannabinoids [22,23,53] S-nitrosylation [33]	NO production [22], Endothelium-dependent vascular relaxation [22,23]
TRPV2	17p11.2	Stretch [59]	Dystrophic cardiomyopathy [69]
TRPV4	12q24.1	Arachidonic acid [25], S-nitrosylation [33], 5′,6′-EETs [8], endocannabinoids [53], cell swelling/shear stress [6,24,54]	Endothelium-dependent vascular relaxation [23,24,25], flow-induced vascular response [6,24], BKca-coupled vascular relaxation [12]
TRPP1–TRPP2	4q21–23	Shear stress [6]	Flow-induced vascular response [6,29,30], NO production [64]

the activation of these channels results in a rise in endothelial $[Ca^{2+}]_i$, which is a crucial second messenger. The mode of TRP channel activation is varied, and involves both capacitative and noncapacitative mechanisms [[5], Table 1]. The capacitative mechanism refers to the Ca^{2+} influx that is stimulated by a reduction in the Ca^{2+} content in intracellular Ca^{2+} stores, whereas the noncapacitative mechanism is independent of Ca^{2+} store depletion. Several signaling molecules, such as diacylglycerol (DAG) [7] and 5,6-epoxyeicosatrienoic acid [8], are found to activate specific TRP isoforms (TRPC3/6/7 and TRPV4, respectively) in endothelial cells independent of store depletion. Regardless of the activation mode, a rise in $[Ca^{2+}]_i$ as a result of TRP channel activation eventually leads to various vascular responses, including changes in vascular tone, alteration in vascular permeability, changes in blood coagulation, vascular remodeling, and oxidative damage. In terms of the second parameter, TRP channels are cation channels that allow the influx of positive ions, such as Na^+ and Ca^{2+}, that results in membrane depolarization. It has been demonstrated that the activity of TRPC3, -C6, and -M4 contributes to membrane depolarization in vascular smooth muscle cells [9–11]. In contrast, the activation of another TRP channel, TRPV4, is found to hyperpolarize the membrane in vascular smooth muscle cells. In this instance, Ca^{2+} influx through TRPV4 channels stimulates Ca^{2+}-sensitive K^+ channels in the vascular smooth muscle cells to cause subsequent smooth muscle hyperpolarization [12]. It is likely that this type of coupling between certain TRP isoforms and Ca^{2+}-sensitive K^+ channels may also exist in endothelial cells, because the agonist-induced Ca^{2+} influx in endothelial cells is usually accompanied by

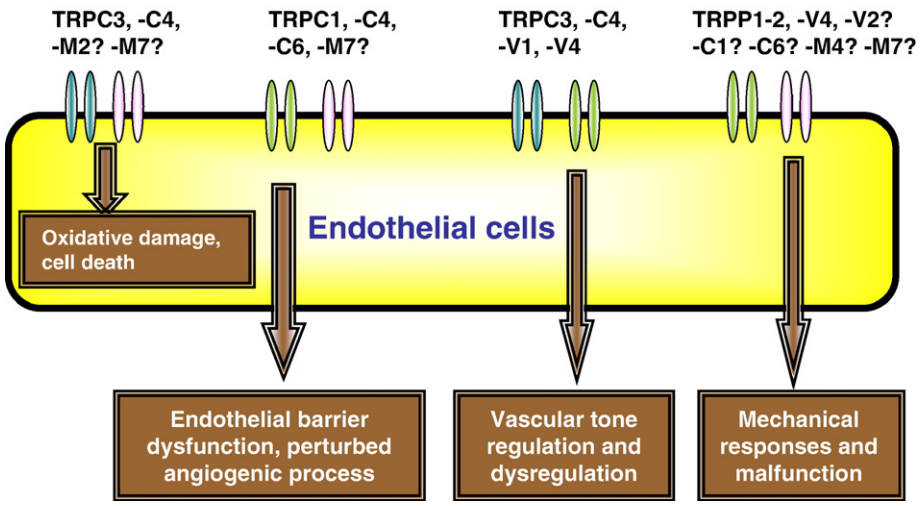

Fig. 1. Schematic figure illustrating the linkage between specific endothelial cell TRP isoforms and possible vascular function and dysfunction.

membrane hyperpolarization [13]. Functionally, the changes in membrane potential that result from TRP channel activity may ultimately alter the driving forces for Ca^{2+} entry to endothelial cells, with hyperpolarization enhancing the Ca^{2+} influx and depolarization reducing it [13]. Furthermore, changes in the membrane potential of endothelial cells may also directly spread to underlying vascular smooth muscle layers through myoendothelial gap junctions, if these are present, and subsequently influence the membrane potential of smooth muscle cells, resulting in an alteration in vascular tone [6].

Because TRP channels play a critical role in endothelial function, it is not surprising that the dysregulation of TRP channel expression or activity may result in endothelial dysfunction and vascular disease. Evidence shows that TRPC1, -C4, and -C6 are associated with endothelial barrier dysfunction [7,14–18]; TRPC3 and -C4 may contribute to oxidative stress-induced endothelial damage [19,20]; TRPC4, -V1, and -V4 are involved in the regulation and dysregulation of endothelium-dependent vascular relaxation [21–25]; TRPC1, -C3, and -C6 may participate in angiogenesis [7,26–28]; and TRPV4 and the TRPP1–P2 complex may participate in flow-induced vascular tone change [24,29,30]. In the following, we summarize a large body of evidence that links TRP channels to endothelial function and dysfunction (Table 1, Fig. 1).

3. Endothelial TRP channels and dysfunction in vascular tone control

One of the most important functions of the endothelium is to regulate vascular tone. Indeed, an impairment in vascular relaxation is commonly used as an index for endothelial dysfunction [2]. Vascular endothelial cells are exposed to numerous endogenous vasoactive agents, such as ATP, histamine, angiotensin II, and substance P, which are either contained in circulating blood or released from vascular cells. These compounds bind to their respective membrane receptors and elicit a rise in endothelial $[Ca^{2+}]_i$, which in turn enhances the production and release of a number of vasodilators, including NO, prostacyclin, and endothelium-dependent hyperpolarizing factors [2,31]. The basal release of NO from endothelial cells appears to be a Ca^{2+}-independent process, but a rise in $[Ca^{2+}]_i$ stimulates endothelial NO synthase, thereby increasing the production and release of NO from endothelial cells [31].

Studies have demonstrated that vasoactive agents may act on TRP channels to modulate endothelial $[Ca^{2+}]_i$ levels (Table 1). For example, TRPC4 is activated by acetylcholine in mouse aortic endothelial cells [21]; TRPC6 is stimulated by bradykinin in cultured mouse heart microvessel endothelial cells [32]; and TRPC5 is activated by ATP in cultured bovine aortic endothelial cells [33]. Note that although only a few TRP channel isoforms have actually been shown to be activated by specific agonists in endothelial cells, it is likely that future research will identify more TRP isoforms that are responsive to vasoactive agonists, because many TRP isoforms share similar activation mechanisms [6].

Because of the pivotal importance of TRP channels in mediating Ca^{2+} influx in response to vasoactive agents, it is not surprising that an alteration in TRP channel expression may impair endothelium-dependent vascular relaxation. TRPC4 perhaps offers the best example of this. TRPC4 mediates agonist-induced Ca^{2+} influx through both the capacitative [21] and noncapacitative mechanisms [34]. In mice that lack TRPC4, agonist-induced Ca^{2+} entry in aortic endothelial cells is dramatically diminished [21], and as a consequence endothelium-dependent vascular relaxation in response to vasoactive agents ATP and acetylcholine is also impaired [21]. These data provide compelling evidence that the diminished functioning of TRPC4 may impair agonist-induced vascular relaxation. There is also an indication that at least two other endothelial TRP channels, TRPV1 and -V4, may be important in agonist-induced vascular tone change [22–25]. In the isolated rat mesenteric bed, the activation of TRPV1 either by cannabinoid anandamine or capsaicin elicits an acute release of NO from endothelial cells, an action that can be reduced by the TRPV1 receptor antagonists 5-iodoresiniferatoxin, SB 366791, and capsazepine [22]. In human cerebral artery endothelial cells, the stimulation of TRPV1 by 2-arachidonoyl-glycerol increases the influx of Ca^{2+}, which activates two important enzymes for vascular dilation, namely, protein kinase G and protein kinase A. This action is indicated by enhanced phosphorylation of vasodilator-stimulated phosphoprotein [23], which is a selective substrate for these two kinases. For TRPV4, it has been shown that 4α-phorbol-12,13-didecanoate and arachidonic acid can activate this channel in endothelial cells, causing endothelium-dependent vascular relaxation in rat coronary and cerebral arteries [24,25]. Note that although these results suggest that TRPV1 and -V4 play an important role in the control of vascular tone, it is yet to be demonstrated that the altered function of these channels can directly impair agonist-induced vascular relaxation. However, there is evidence that reduced TRPC4 activity can impair flow-induced vascular relaxation, an issue that will be further discussed later.

As has been mentioned, the malfunction of TRP channels may impair Ca^{2+} influx, causing a reduction in NO bioavailability and the subsequent impairment in vascular relaxation. Interestingly, recent studies suggest that NO itself may modulate TRP channels activity through feedback mechanisms. NO may activate multiple TRP isoforms, including TRPC5, -V1, -V3, and -V4, by cysteine S-nitrosylation [33]. However, NO and its downstream signal molecules cGMP and protein kinase G can also inhibit several TRP isoforms in endothelial cells, such as TRPC3, -C6, -M4, in a negative feedback manner [35,36]. These feedback mechanisms may act as NO sensors that allow endothelial NO levels to be finely regulated. The dysregulation of these pathways may therefore disturb the NO balance, resulting in endothelial dysfunction.

4. Endothelial TRP channels and oxidative stress

Oxidative stress describes the cell injury that results from the increased formation of reactive oxygen species (ROS) and/or the decreased antioxidant reserves. The physiological production of ROS is necessary for the maintenance of cell homeostasis, but the excessive production of ROS results in

cell injury [2,37]. Endothelial cells are constantly exposed to ROS that are released from neutrophils, macrophages, and vascular smooth muscle cells [2,38]. Moreover, endothelial cells are themselves generators of ROS [2,38]. The main ROS that are produced are superoxide anions, hydroxyl radicals, peroxynitrite, and H_2O_2. ROS may arise from the activity of NADPH oxidase, xanthine/xanthine oxidase, uncoupled NO synthase, and mitochondrial respiration. In pathological states or stress conditions, such as inflammation, hyperglycemia and ischemia/reperfusion, ROS are produced in excessive amounts [2,38]. These excess ROS react with endothelial macromolecules to cause extensive damage to the structure and function of endothelial cells. For example, superoxide anions reduce the bioavailability of NO by scavenging NO and inhibiting the expression of endothelial NO synthase, which results in the impairment of endothelium-dependent vascular relaxation and abnormal leukocyte adhesion and platelet aggregation onto the surface of endothelial cells [2,38]. Furthermore, the overproduction of ROS also induces endothelium-dependent contractions [2]. Such ROS-induced endothelial dysfunction may eventually contribute to the pathogenesis of many vascular diseases, including atherosclerosis, hypertension, and heart failure [38].

ROS-induced endothelial dysfunction is often preceded by an alteration in endothelial $[Ca^{2+}]_i$, which may result from ROS action on plasma membrane channels, $InsP_3$-receptors, endoplasmic reticulum Ca^{2+}-ATPase, or other Ca^{2+} signaling pathways [6,20]. Recent evidence indicates that TRP channels are important targets for ROS [19,20,39,40]. These ROS-sensitive TRP channels may potentially act as endothelial cell sensors for oxidative stress, an interaction that may have very significant physiological and pathological consequences [6,20]. Furthermore, the ability to downregulate these channels may be a means of protecting endothelial cells from oxidative stress-induced cell injury.

Two TRPC channels, TRPC3 and -C4, are activated by oxidative stress. Balzer et al. [19] show that the oxidant tert-butylhydroperoxide activates TRP-like cation conductance in porcine aortic endothelial cells. The expression of an N-terminal fragment of human TRPC3, but not of a C-terminal fragment, abolishes the oxidant-induced cation current, suggesting that TRPC3 is a component of oxidant-activated cation channels in endothelial cells. A follow-up study by the same research group demonstrates that the oxidant-activated TRPC3 cation conductance in TRPC3-overexpressing HEK cells and porcine aortic endothelial cells is inhibited by dominant negative mutants of TRPC4 [20]. The authors conclude that TRPC3 and -C4 may form redox-sensitive heteromeric channels that are the molecular basis of oxidant-activated cation channels in porcine aortic endothelial cells [20].

TRPM2 and -M7 are also activated by oxidative stress [37,39,40] and are both expressed in endothelial cells [6], but there is still a lack of evidence of the functional role of these channels in endothelial cells. However, in several other cell types, TRPM2 and -M7 play a role in ROS-induced cell injury. For instance, TRPM2-transfected HEK293 cells display an oxidative stress-induced $[Ca^{2+}]_i$ rise and an increased susceptibility to cell death [39]. In rat insulinoma RIN-5F cells, the suppression of TRPM2 expression with antisense oligonucleotides significantly reduces ROS-induced cell death [39]. In monocytic cell line U937-ecoR, oxidative stress increases the expression level of TRPM2 with an associated decrease in cell viability, and the suppression of endogenous TRPM2 either by RNA interference or dominant negative splice variant reduces the cell death that is induced by H_2O_2 [41]. In cortical neurons, the suppression of TRPM7 expression with RNA interference blocks TRPM7-like currents, anoxic Ca^{2+} uptake, and anoxic neuronal cell death [40]. Collectively, these data suggest that TRPM2 and -M7 have an important functional role in oxidative stress-induced cell injury. However, future studies are needed to determine whether these two channels also play a role in oxidative stress-induced endothelial damage.

5. TRP channels and endothelial barrier dysfunction

The endothelial cell layer forms a semi-permeable dynamic barrier between the vascular space of blood vessels and underlying tissues. Endothelial cells tightly adhere to each other, which helps to maintain the integrity of the vessel wall and control the passage of plasma proteins and solutes. 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 [16]. Therefore, an increase in the contraction force or decrease in the adhesive force enlarges the interendothelial gap, resulting in the loss of the selective vascular barrier to circulating macromolecules [16].

Inflammatory cytokines, viruses, and growth factors act on the endothelial barrier to initiate a cascade of events that lead to vascular leakage and vascular edema [16]. One of the early events in this signaling cascade is a rise in endothelial $[Ca^{2+}]_i$. After binding to their respective receptors, growth factors activate phospholipase C-γ and inflammatory mediators stimulate phospholipase C-β. The activity of phospholipase C produces $InsP_3$, causing subsequent release of stored Ca^{2+}, which in turn stimulates capacitative Ca^{2+} influx [16]. The rise in $[Ca^{2+}]_i$ then activates key signaling pathways, which results in myosin light chain-dependent endothelial cell contraction, actin polymerization, and the disassembly of vascular endothelial cadherin at the adherens junctions [16]. These events eventually lead to endothelial barrier dysfunction [16].

The rise in $[Ca^{2+}]_i$ is a requisite for endothelial barrier dysfunction [16]. Several TRP channels, including TRPC1, -C4, and -C6, are implicated in endothelial barrier dysfunction. For instance, increasing the expression of TRPC1 either by challenging endothelial cells with tumor necrosis factor-α or by TRPC1-cDNA transfection results in excessive Ca^{2+} influx, which exaggerates the thrombin-induced increase in actin-stress fiber formation and leads to endothelial barrier dysfunction [14]. Thrombin is an inflammatory mediator that activates TRPC1. The resultant Ca^{2+} influx in turn stimulates TRPC1 protein synthesis, which causes further Ca^{2+} influx to form a positive feed-forward loop [15]. The excessive Ca^{2+} influx that is generated from this positive feed-forward loop is suggested to be a cause of endothelial barrier dysfunction [15].

TRPC4 is another channel that plays an important role in endothelial barrier function and dysfunction. The activation of TRPC4 requires protein 4.1, which tethers the channel to the membrane skeleton and forms the gating mechanism that is required for Ca^{2+} permeation [18]. Like TRPC1, TRPC4 also contributes to capacitative Ca^{2+} influx [16–18]. There is evidence that TRPC4 and -C1 actually form heteromultimeric channels that may be the molecular basis of a capacitative Ca^{2+} channel in endothelial cells [42]. It is known that excessive capacitative Ca^{2+} influx in endothelial cells, which is likely due to the activity of TRPC1 and -C4, triggers cytoskeletal reorganization, eventually leading to the disruption of the endothelial barrier [16,43]. In contrast, the suppression of capacitative Ca^{2+} influx through the deletion of the TRPC4 gene can blunt thrombin-induced actin stress fiber formation and cell retraction [16], thereby reducing the thrombin-induced increase in vascular permeability [16].

TRPC6 may also be involved in endothelial barrier dysfunction. In frog mesenteric microvessels, vascular endothelial growth factor (VEGF)-induced increases in vascular permeability can be mimicked by 1-oleoyl-2-acetylglycerol, an activator of the TRPC3/6/7 subfamily of channels [7]. Furthermore, flufenamic acid, which activates TRPC6 but inhibits -C3 and -C7, enhances the VEGF-induced increase in vascular permeability. These data suggest that TRPC6 has a role in VEGF-mediated vascular barrier dysfunction [7].

6. Endothelial TRP channels and the perturbed angiogenic process

Angiogenesis is a process of new vessel formation during which vascular growth factors, such as VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and transforming growth factors, increase vascular permeability, facilitate the breakdown of the extracellular matrix, and stimulate the migration and proliferation of endothelial cells [44]. Angiogenesis occurs under physiological conditions, such as vessel growth and repair, and pathological conditions, such as neovascularization at the sites of tumors. Atherosclerosis can also be considered to be an angiogenesis-associated disease, because many studies have shown that intimal neovascularization is associated with plaque development and instability [45]. Endothelial cells play an essential role in the angiogenic process. Endothelial dysfunction with reduced NO bioavailability may impair normal angiogenesis in physiological conditions, thus delaying vessel repair after damage and causing insufficient neovascularization at ischemic sites [46]. A dysfunctional endothelium may also contribute to intimal neovascularization in atherosclerotic plaques [46].

TRP channels may affect the angiogenic process through several mechanisms. First, angiogenic growth factors such as VEGF and bFGF may activate TRP channels, causing a subsequent rise in endothelial $[Ca^{2+}]_i$, which modulates the signal transduction pathways and leads to angiogenesis [6,31]. In this aspect, it has been found that TRPC1 is involved in bFGF-induced Ca^{2+} influx in bovine aortic endothelial cells [26]; TRPC6 contributes to VEGF-induced Ca^{2+} influx in frog mesenteric microvessels endothelial cells [7]; and TRPC3 and -C6 mediate VEGF-induced Ca^{2+} influx in human microvascular endothelial cells *in vivo* [27]. Second, Ca^{2+} influx through TRP channels may stimulate endothelial cells to produce and release the angiogenic growth factors VEGF and PDGF [6,28], which consequently stimulate angiogenesis. Third, some TRP channels, including TRPM6 and -M7, allow the influx of Mg^{2+}, which is an essential player in endothelial cell proliferation and angiogenesis [6,31,47]. It is possible that TRP channel-mediated $[Mg^{2+}]_i$ influx in response to mitogenic agents may modulate the downstream signal transduction pathways, leading to angiogenic development [6,31,47]. Note that although a substantial amount of data supports the role of TRP in angiogenesis, there is still no direct evidence to show that the dysfunction of endothelial TRP channels can indeed impair normal vessel growth/repair or promote neovascularization during atherosclerotic progression.

7. TRP channels, mechanical responses, and endothelial dysfunction

Blood flow exerts a viscous drag, or shear stress, on the surface of endothelial cells that are aligned in the direction of flow [48]. Endothelial cells exhibit diverse biochemical and physiological responses to shear stress. A high shear flow has been found to increase the endothelial release of NO and prostacyclin; inhibit leukocyte binding and chemoattractant protein expression on endothelial cell surface; reduce the release of growth factors from endothelial cells, thus inhibiting the proliferation of smooth muscle cells; and exert an anti-apoptotic effect on endothelial cells, thus preventing the occurrence of artery lesions [48]. In contrast, a low shear stress and a reversal in the direction of flow may lead to endothelial dysfunction. Manifestations of dysfunctional endothelium can be readily observed in certain areas of the arterial tree, such as branch points, that experience a low mean shear stress and flow reversal [49].

Some of the shear stress-induced responses, such as the regulation of gene expression and the release of NO, are at least partly related to a rise in $[Ca^{2+}]_i$ [50,51], in which flow-sensitive Ca^{2+} channels may play a key role [6,52]. Several endothelial TRP channels, including TRPV4 and the TRPP1–P2 complex, are activated by shear stress [6,53,54]. The dysfunction or dysregulation of these channels may impair flow-induced vascular relaxation. Using a pressure myograph technique, Kohler et al. found that the inhibition of endothelial TRPV4 channels, either with ruthenium red or arachidonyl trifluoromethyl ketone, abolishes the flow-induced vascular relaxation in rat carotid arteries and arteria gracilis [24]. These experiments provide the first evidence that the dysfunction of TRPV4 channels in endothelial cells may impair flow-induced vascular relaxation.

The TRPP1–P2 complex mediates flow-induced Ca^{2+} influx in renal epithelial cells [55]. Nauli et al. propose that TRPP1 and -P2 physically interact with each other to form a mechanosensor that detects fluid flow in renal epithelial cells. Within the complex, TRPP1 serves as a sensor to transduce the flow

stimulus to TRPP2, which is a Ca^{2+} influx channel [55]. TRPP1 and -P2 are both expressed in vascular endothelial cells [6], and evidence suggests that the malfunction of endothelial TRPP1 and -P2 may impair the regulation of NO synthase, resulting in endothelial dysfunction that may contribute to the progress of the common genetic autosomal dominant polycystic kidney disease (ADPKD) [29,30].

A recent study also shows that TRPM7 is sensitive to flow shear stress, and thus plays a role in pathological responses to vessel wall injury [56]. Oancea et al. found that the exposure of vascular smooth muscle cells to flow shear stress facilitates the translocation of TRPM7 proteins to the plasma membrane, which results in an increase in the whole-cell TRPM7 currents. The authors propose that this increased TRPM7 activity may cause smooth muscle cell injury in areas in which smooth muscle cells are exposed to flow, such as in atherosclerotic regions [56]. However, it is not clear whether TRPM7 in endothelial cells has a similar function.

In addition to shear stress-activated channels, endothelial cells also express other mechanosensitive TRP channels, including those activated by membrane stretch directly and those activated by stretch indirectly through cytosolic signaling molecules. The former group includes TRPC1, -C6, and -V2 [57–59], and the latter group includes TRPC6 and -M4. In indirect pathways, it has been shown that TRPM4 can be activated through the mechanosensitive production of DAG or PKC [60], whereas TRPC6 is activated through DAG [9,61]. Interestingly, intravascular pressure can activate TRPC6 by both direct and indirect pathways. Regardless of the details of their activation mechanisms, these mechanosensitive TRP channels are expected to be activated by the pulsatile stretching of the endothelial cell plasma membrane during cardiac cycles. The malfunction of these channels may result in the dysregulation of vascular tone.

8. Endothelial TRP channels and vascular diseases

Endothelial dysfunction is a multifaceted disorder that is associated with many cardiovascular diseases, including hypertension, atherosclerosis, heart and renal failure, coronary syndrome, thrombosis, diabetes, obesity, inflammation, and hypercholesterolemia [2]. Taking hypertension as an example, endothelium dysfunction precedes the onset of high arterial blood pressure in many hypertensive patients [62], who display an increased production of ROS, a decreased availability of NO, and an augmented production of endothelium-derived contracting factors, all of which adversely affect the control of vascular tone [2]. As has been described, endothelial dysfunction may be caused by the malfunction of TRP channels, and it is therefore tempting to suggest that the malfunction of endothelial TRP channels may be a causative factor that contributes to vascular diseases.

Perhaps the strongest evidence for the causative role of endothelial TRP channels in vascular diseases is the TRPP mutations in ADPKD. ADPKD patients present an impaired endothelium-dependent relaxation to acetylcholine in resistance vessels [63]. Moreover, a frequent polymorphism of endothelial NO synthase, Glu298Asp, has been found to be associated with renal disease progression in ADPKD patients [64]. In animal studies, TRPP1 heterozygous mice ($TRPP1^{+/-}$) also display an impairment in endothelium-dependent vascular relaxation, and TRPP1 knockout mice display the pathogenesis of vascular fragility, edema, and localized hemorrhages [29,65]. Collectively, these data suggest that the malfunction of endothelial TRPP1 and -P2 impairs the complex regulation of endothelial NO synthase, which results in endothelial dysfunction and contributes to the progression of ADPKD [30].

In addition to TRPP1–P2 complex, the dysfunction or dysregulation of other TRP channels may also contribute to cardiovascular diseases. For example, the expression level of TRPC3 and -C5 in monocytes is increased in patients with essential hypertension [66]; there is an increased expression of TRPC3 and -C6 in pulmonary artery smooth muscle cells in patients with idiopathic pulmonary arterial hypertension [67]; and the expression level of TRPC5 channels is abnormally elevated in the failing human heart [68]. In addition, the overexpression of TRPV2 has been suggested to be responsible for cardiac muscle degeneration in patients with dystrophic cardiomyopathy [69]. Interestingly, a recent study has explored the therapeutic potential of targeting TRPC1 and finds that inhibiting TRPC1 with a blocking antibody results in a significant reduction in neointimal growth in the human saphenous vein [70]. These data suggest the possibility of targeting TRPC1 for the therapeutic treatment of occlusive vascular diseases such as atherosclerosis [70]. However, note that in most of the aforementioned cases, the TRP channels that reside in vascular smooth muscle cells or cardiac myocytes are believed to be the culprits, and it is not clear whether the dysfunction of endothelial TRP channels may also contribute to the pathogenesis of these diseases. Nevertheless, due to the close association between cardiovascular diseases and endothelial dysfunction, it would not be a surprise if future studies find a link between these diseases and endothelial TRP dysfunction.

9. Concluding remarks

The dysfunction and dysregulation of endothelial TRP channels are suggested to result in excessive oxidative damage, decreased NO availability, the disruption of the endothelial barrier, and the progression of angiogenesis-associated diseases (Table 1). However, the field of TRP channels is rapidly evolving, and many areas of uncertainty remain. Direct links between TRP channels and endothelial dysfunction have been convincingly demonstrated in only a very small number of cases, and therefore the roles of many TRP channels in endothelial dysfunction and vascular diseases remain largely speculative. Obviously, we are still in the initial stage of considering endothelial TRP channels as targets for novel therapeutic intervention, and further study is needed to achieve definite and detailed answers regarding the role of different TRP isoforms in endothelial dysfunction. Because of the lack of specific pharmacological inhibitors for many TRP channel isoforms, other molecular biological techniques, such as gene knockout mice and small-interference RNA-mediated gene-

silencing technology, may be particularly useful for the elucidation of the role of TRP channels in endothelial dysfunction. Genetic linkage analysis in patients with ion channelopathy should further help to reveal the pathological consequences of TRP channel dysfunction and dysregulation.

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