TRPC Channels in Health and Disease

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Abstract

This chapter offers a brief introduction of the functions of TRPC channels in non-neuronal systems. We focus on three major organs of which the research on TRPC channels have been most focused on: kidney, heart, and lung. The chapter highlights on cellular functions and signaling pathways mediated by TRPC channels. It also summarizes several inherited diseases in humans that are related to or caused by TRPC channel mutations and malfunction. A better understanding of TRPC channels functions and the importance of TRPC channels in health and disease should lead to new insights and discovery of new therapeutic approaches for intractable disease.

Keywords

TRPCs • Kidney • Cardiovascular • Lung

With the fact that TRPC channels are universally expressed in most of the major organs, it is not surprising that they contribute to normal development, and their malfunction leads to diseases of these organs. We will discuss in depth the physiological and pathological functions of TRPC channels in nervous system in the following chapters. In this chapter, we will give a general introduction of the roles of TRPC channels in the kidney, cardiovascular system, and lung, the three major organs that the functions of TRPC channels have been most extensively studied in the past decades.

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4.1 TRPCs in Kidney Health and Disease

The key function of the kidney is to filter the plasma to dispose metabolic end products, excess electrolytes, and water. It is accomplished by a structure called glomerulus or renal corpuscle. The glomerulus is the functional blood filtration unit and is the first component involved in regulating the composition of urine. Disruption of the glomerular filtration barrier is a common outcome of many kidney diseases, including focal segmental glomerulosclerosis (FSGS), diabetic nephropathy, and lupus nephritis [1]. Proteinuria is a hallmark of dysfunction of glomerular filtration barrier [2]. Persistent dysfunction leads to progressive renal failure and needs for dialysis or kidney transplantation.

The basic unit of the glomerulus tuft is a single capillary with the glomerular basement membrane (GBM) as primary structure scaffold. Endothelial and mesangial cells providing capillary support are located inside GBM, whereas podocytes are attached to the outside the GBM. There are thus four major cell types in the glomerulus: endothelial cells, mesangial cells, parietal epithelial cells of Bowman's capsule, and podocytes. The expression of TRPC channels has been found mostly in mesangial cells and podocytes in the glomerulus. Several lines of evidence show that TRPC1, TRPC3, TRPC4, TRPC5, and TRPC6 were all expressed in the kidney [3–8]. TRPC1 is exclusively expressed in mesangial cells, whereas TRPC3 and TRPC6 have broader expressions. TRPC3 and TRPC6 are confined to podocytes and mesangial cells. They are also expressed in the collecting duct which connects the nephrons to the ureter. In the following part of this chapter, we will provide an overview of the current knowledge of TRPC channels on mesangial cells and podocytes and functions of TRPC channels in the collecting duct which plays an important role in reabsorption and excretion.

4.1.1 TRPCs in Mesangial Cells

Mesangial cells are specialized cells around blood vessels in glomerulus. Major functions of mesangial cells are to remove trapped residues and aggregated protein from the GBM, thus keeping the filter free of debris. They are contractile cells that regulate filtration rate by altering surface area of the capillaries. Ca^{2+} influx across the plasma membrane is critical for mesangial cell contraction in response to vasoactive peptides. Altered responses of mesangial cells to vasoactive peptides is one of the major causes that leads to various renal diseases, such as diabetic nephropathy [9]. Several types of Ca^{2+} channels are involved in this physiological process. These channels include voltage-gated Ca^{2+} channels, receptor-operated Ca^{2+} channels, and store-operated Ca^{2+} channels [10–14]. Both TRPC1 and TRPC4 are key components of store-operated Ca^{2+} channels in mesangial cells [5]. TRPC1 contributes to contractile function of mesangial cells by mediating vasoconstrictor-stimulated Ca^{2+} responses, whereas TRPC4 is activated by store depletion. In high glucose-treated cultured mesangial cells, an in vitro model for diabetes, TRPC6 expression is reduced. TRPC6 knockdown in high glucose-treated mesangial cells shows reduced Ca^{2+} entry in response to angiotensin II, suggesting that deficiency of TRPC6 might contribute to the impaired Ca^{2+} signaling of mesangial cells seen in diabetes [7, 15, 16].

Mesangial cell proliferation and apoptosis are involved in the maintenance of glomerular integrity. Perturbation of glomerular integrity provides pathophysiological mechanisms that underlie kidney disease. Mesangial cell excessive proliferation and extracellular deposition is a pathological condition commonly found in chronic kidney diseases. Mesangial cell apoptosis contributes to the resolution of glomerulosclerosis [17]; however, it is associated with proteinuria and hypertension in diabetic nephropathy [18]. TRPC6 activation has been shown to be involved

in inhibiting proliferation and triggering apoptotic cell death in primary neonatal pig mesangial cells. It is achieved by induction of calcineurin/NFAT, FasL/Fas, and caspase signaling cascade [19]. Interestingly, angiotensin II, which can stimulate mesangial cell proliferation, affects TRPC6 protein level and distribution [20]. Nevertheless, whether angiotensin II-stimulated mesangial cell proliferation is mediated by Ca^{2+} influx through TRPC6 needs to be further validated.

4.1.2 TRPCs in Podocyte

Podocytes are pericyte-like cells with a complex cellular organization consisting of a cell body, major processes, and foot processes. Their foot processes elaborate into a characteristic pattern with foot processes of neighboring podocytes, forming in between the filtration slits. Podocyte foot processes play a major role in establishing the selective permeability of the glomerular filtration barrier [21]. Therefore, podocyte injury is associated with marked albuminuria [22].

Disruption of Ca^{2+} signaling and homeostasis were postulated as early events in podocyte injury. Since TRPC6 mutations are found in patients with FSGS, the molecular mechanisms involving TRPC channels have been studied extensively in podocyte biology [13]. Within podocytes, TRPC6 appears to localize in both major processes and foot processes, and at least some TRPC6 colocalizes to the slit diaphragm (SD), suggesting that it is the abnormal function of TRPC6 within the podocyte that ultimately leads to disease in families with FSGS-associated TRPC6 mutations [12]. Mounting evidences have been shown that proteinuria and podocyte foot processes effacement are mediated by rearrangement of the actin cytoskeleton [23]. Recently, angiotensin receptor-activated TRPC5 and TRPC6 channels have been shown as antagonistic regulators of actin dynamics and cell motility through the regulation of Rac1 and RhoA, respectively [24, 25]. The later study shows that inhibition of TRPC6 results in the loss of stress fibers, Rac1 activation, and increased mobility. On the contrary, inhibition of TRPC5 leads to enhanced stress fiber formation, RhoA activation, and decreased motility. Thus, there are two distinct signaling microdomains emerged in podocytes, one with the TRPC5 which specifically interacts with and activates Rac1 and the other with TRPC6 specifically interacts with and activates RhoA. Consistent with previous studies, CsA restores synaptopodin expression in TRPC6-depleted cells, whereas synaptopodin expression is preserved in TRPC5-depleted podocytes [6, 26].

Transgenic mice overexpressing wild-type TRPC6 and TRPC6 gain-of-function mutants develop albuminuria and FSGS-type lesions [27]. In keeping with this, TRPC6 knockout mice are protected from the proteinuria effects of angiotensin II [28]. In the light of the antagonistic effects of TRPC5 and TRPC6 on podocyte actin dynamics, one would assume that they might have opposite effect in the biology of proteinuria development. Surprisingly, a recent study has shown that depletion of TRPC5 or pharmacological inhibition of TRPC5 protects mice from proteinuria [6]. One possible explanation is that the motility of the foot processes needs to be increased fast enough in response to environmental changes but also to be stable enough in the stationary state. Breaking the balance in either direction will lead to leakage of the filter.

4.1.3 TRPCs in Collecting Duct

The collecting duct of the kidney connects the nephron to the ureter. It plays a role in electrolyte and fluid balance through reabsorption and secretion. Both TRPC3 and TRPC6 are expressed in the principle cells of the collecting duct [8, 10]. TRPC3 is primarily localized to the apical membrane, whereas TRPC6 is found in both apical and basolateral domains. Diffuse TRPC3 and TRPC6 are also found in cytoplasm, presumably localized to intracellular vesicles. Arginine-vasopressin (AVP), which is an antidiuretic hormone that controls water homeostasis and urine concentration by controlling water reabsorption in the collecting duct, can selectively translocate

TRPC3, but not TRPC6, to the apical membrane [29]. Furthermore, AVP-induced increase of intracellular Ca^{2+} is attenuated by expressing a dominant-negative TRPC3. These results suggest that TRPC3 targeting to the apical membrane in collecting duct principle cells can contribute to the AVP-induced Ca^{2+} reabsorption in this region of nephron [29].

4.2 TRPCs in Heart and Vasculature

Like in other tissues, Ca^{2+} plays an important role in maintaining the physiological functions of cardiovascular system, such as cardiac contractility, hemodynamic stretch, dilatation, and repair. TRPC channels, which are ubiquitously expressed in almost all cell types in heart and vasculature, work with other membrane receptors and ion channels to regulate intracellular calcium concentration spatiotemporally. Dysfunctions of TRPC channels are involved in many types of cardiovascular diseases; therefore, TRPC channels have been proposed as therapeutic targets for drug development [30, 31].

4.2.1 TRPCs in Heart

TRPC channels are localized to the peripheral plasma membrane in cardiomyocytes. It is reported that the expression and activation of TRPC channels are both increased during cardiac hypertrophy and heart failure. In cultured cardiomyocytes and in vivo models, the hypertrophic factors, such as endothelin-1 (ET-1), angiotensin II (Ang II), or pressure overload, increase the expression of TRPC1 [32, 33] and TRPC3 [34]. In animal models, upregulation of TRPC1 and TRPC7 is observed in myocardium of Dahl salt-sensitive hypertensive rats [33, 35]. In human patients, the expression of TRPC6 is increased in cardiac hypertrophy and heart failure [36], and TRPC5 is found to be increased in human failing heart samples [34]. Cardiac hypertrophy is a thickening of myocardium which results from several pathological conditions, such as hypertension, excess neurohormones, valvular abnormalities, and myocardial infarction remodeling. Dysregulation of Ca^{2+} is one of the mechanisms proposed to be involved in formation of cardiac hypertrophy. The substantial and low increased of $[Ca^{2+}]_i$ elicited by SOCE or ROCE activates calcineurin, a calcium and calmodulin-dependent serine/threonine protein phosphatase, which dephosphorylates nuclear factor of activated T cell (NFAT). Subsequently, activated NFAT translocates into nucleus and induces the transcription of several hypertrophic genes [37]. Recent studies suggest that TRPC channels are responsible for the substantial and low increased of $[Ca^{2+}]_i$ elicited by SOCE or ROCE in cardiomyocyte and contribute to cardiac hypertrophy through Calcineurin-NFAT pathway [38].

In hypertrophied myocytes, the expression of TRPC1 and $[Ca^{2+}]_i$ induced by SOCE are both significantly increased compared to normal myocytes [33]. Overexpression of TRPC1 in cultured cardiomyocytes elevates $[Ca^{2+}]_i$ elicited by SOCE and activates calcineurin/NFAT pathway [33]. *Trpc1* gene silencing inhibits NFAT activation and 5-HT2A receptor-mediated hypertrophic response induced by ET-1 and Ang II [39]. Moreover, $TRPC1^{-/-}$ mice was protected from cardiac hypertrophy and maintained preserved cardiac function after hemodynamic stress and excess neurohormone insults [32]. In contrast, transgenic mice with cardiomyocyte-specific expression of TRPC3 or TRPC6 show enhanced calcineurin/NFAT signaling and are more sensitive to pressure overload or agonist-induced cardiac hypertrophy [36, 40]. Additionally, the hypertrophic phenotype in TRPC3 transgenic mice was abolished by deletion of the *calcineurin A* gene, which further supports the idea that the hypertrophic effect of TRPC channels is associated with enhanced calcineurin/NFAT signaling [41]. Interestingly, it is found that NFAT also increases the expression of TRPC1, TRPC3, and TRPC6 to form a positive feedback loop, which is proposed to be involved in the development of cardiac hypertrophy [33, 34, 36]. Transgenic mice with a dominant-negative form of TRPC3 or TRPC6 show attenuated hypertrophic response after pressure overload or neurohormone stimu-

lations [38]. Consistently, a new report shows that phenylephrine (PE) that caused pathologic cardiac hypertrophy in wild-type mice was prevented by deletion of TPRC3 gene [42]. In addition, deletion of *trpc6*gene prevents stress-induced exaggerated cardiac remodeling in Klotho-deficient mice [43]. Moreover, TRPC3/TRPC6 antagonists (GSK2332255B and GSK2833503A) block cell hypertrophy in neonatal and adult cardiac myocytes following ET-1 or Ang II stimulation in a dose-dependent manner [44], and TRPC3-selective inhibitor Ryr3 attenuates cardiac hypertrophy in mice subjected to pressure overload [45]. The N-terminal fragment of TRPC4, which disturbs the functions of TRPC4 homomeric and TRPC4/TRPC5 heteromeric channels, protects the mice from hypertrophic stimulations [38, 46]. All these findings raise the possibility that TRPC channels might serve as therapeutic targets to prevent cardiac hypertrophy.

Over time, hypertrophic heart eventually ends up with heart failure. Though the transition from cardiac hypertrophy to heart failure is not clear, myocardial apoptosis is proposed to be an important step in between. Intracellular Ca^{2+} overload induces apoptosis in many cell types. It is reported that overexpression of TRPC3 increases apoptosis in adult mouse cardiomyocytes subjected to ischemia-reperfusion [47], which suggests that TRPC3 may be involved in heart failure. Besides TRPC3, TRPC7 acts as a G protein-activated Ca^{2+} channel mediating Ang II-induced myocardial apoptosis [35]. The expression level of TRPC7 and cell apoptosis increased simultaneously in the failing myocardium of Dahl salt-sensitive hypertension rats, and temocapril, an angiotensin-converting enzyme inhibitor, suppressed both [35]. Inconsistent with previous reports, TRPC7, unlike its close homologues TRPC3 and TRPC6, undergoes remarkable downregulation during the establishment of cardiac hypertrophy [48]. Furthermore, TRPC6 activation might suppress heart failure via inhibition of myofibroblast differentiation [49]. Thus, how TRPC channels involved in the transition from cardiac hypertrophy to heart failure still need to be further investigated.

4.2.2 TRPCs in Vasculature

The extracellular Ca^{2+} entrance in vascular smooth muscle cells (VSMC) and endothelial cells regulates various functions in pulmonary and systematic circulation, such as artery remodeling, vasoconstriction, and vasodilatation. All subunits of TRPCs are expressed in VSMC and vascular endothelial cells to form functional channels that are permeable to Ca^{2+}, which suggests that TRPC channels may also play important roles in vascular system [50–52].

Abnormal VSMC proliferation in vascular remodeling is associated with development of hypertension and atherosclerosis [53]. It is shown that the elevation of $[Ca^{2+}]_i$ is critical for VSMC growth. Chelating extracellular or intracellular Ca^{2+} both inhibit the cell proliferation [54]. Upregulation of TRPC1and TRPC4 has been reported in VSMC and contributes to cell growth subjected to various stimulation, such as Ang II, ATP or pressure load insults, by phosphorylation of cyclic AMP response element-binding protein (CREB) through elevation of $[Ca^{2+}]_i$ [55, 56]. Excessive proliferation of pulmonary artery smooth muscle cell (PASMC) has been observed in patients with idiopathic pulmonary arterial hypertension (IPAH). The expression of TRPC3 and TRPC6 is increased in PASMC in the pulmonary artery tissue from IPAH patients. Downregulating the expression of TRPC6 by siRNA attenuates cultured PASMC proliferation from IPAH patients [57]. However, deletion of TRPC6 does not protect mice from chronic pulmonary hypertension and vascular remodeling [58]. Besides, TRPC1 is thought to be critical for cell proliferation in human PASMC from non-pulmonary hypertension [55, 59].

VSMC contraction caused by Ca^{2+} entry through Ca^{2+} permeable channels is important for regulation of blood pressure. Attenuating the function of TRPC1 by anti-TRPC1 antibody inhibits the SOCE-induced cell contraction. Consistently, overexpression of TRPC1 in rat pulmonary artery increases $[Ca^{2+}]_i$ elicited by SOCE and promotes contraction [60]. It's also reported that TRPC6 is the essential component of vascular α_1-adrenoceptor-activated Ca^{2+}-permeable

cation channel in rabbit portal vein smooth muscle cell (SMC). SMC contraction induced by α_1-adrenergic agonists can be blocked by suppressing TRPC6 expression [61]. In addition, activation of TRPC6 has been found in vasopressin, a vasoconstrictor, stimulated A7r5 aortic SMC [62]. Unexpectedly, TRPC6$^{-/-}$ mice show elevated blood pressure, hyperactivity of airway smooth muscle cells, and increased contractility in isolated tracheal and aortic rings [63, 64]. Furthermore, SMC from TRPC6$^{-/-}$ aorta or cerebral arteries are more depolarized with enhanced spontaneous and agonist-induced Ca^{2+} entry [63]. These phenomena can be explained by compensatory expression of constitutive active TRPC3 channels in TRPC6$^{-/-}$ mice. It is reported that UTP-induced depolarization of rat cerebral arteries and subsequent contraction of SMC can be blocked by suppressing the expression of TRPC3, not TRPC6, in these cells [65]. In spontaneous hypertension rats, the expression of TRPC3 is abnormally high compare with normotensive Wistar-Kyoto rats [66]. ET-1, which also works as potent vasoconstrictor in controlling blood pressure, activates aCa^{2+}-permeable cation channel with TRPC7 and TRPC3 in rabbit coronary artery myocytes [67]. Regional alveolar hypoxia induces constriction of pulmonary arteries and redirects blood flow to alveoli with higher oxygen content to ensure maximal oxygenation of the venous blood [68]. The phenomenon is called hypoxic pulmonary vasoconstriction, and $[Ca^{2+}]_i$ elevation is suggested to play a key role in this process [69]. TRPC6$^{-/-}$ mice completely lost acute hypoxic pulmonary vasoconstriction, and hypoxia-induced $[Ca^{2+}]_i$ elevation is absent in PASMC of TRPC6$^{-/-}$ mice [58]. Upregulation of TRPC1 and TRPC6 has been reported in hypoxic pulmonary arteries accompanied with increased $[Ca^{2+}]_i$ elevation induced by SOCE or ROCE as well as the basal level of $[Ca^{2+}]_I$ [70]. The increased expression level of TRPC1 and TRPC6 in PASMC is mediated by the activation of oxygen-sensitive transcription factor hypoxia-inducible factor 1 (HIF1) [71].

Endothelial cells are involved in many aspects of vascular biology such as barrier function, angiogenesis, vasoconstriction, and vasodilatation. The endothelium acts as a semi-selective barrier between the vessel lumen and surrounding tissue. Chronic inflammation in vessels changes the shapes of endothelial cells and increases the permeability of endothelium which may lead to tissue edema or swelling [72]. It's suggested RhoA activation and Ca^{2+} entry through TRPC1, TRPC4, and TRPC6 channels both contribute to the thrombin-induced increase in endothelial cell contraction, to the cell shape change, and consequently to the mechanism of increased endothelial permeability [73–75]. TRPC1, TRPC3, and TRPC6, together with vascular epithelial growth factor (VEGF) receptor 2, mediate VEGF-induced Ca^{2+} entry and permeability of human microvascular endothelial cells [76, 77]. TRPC6 channels mediate VEGF-induced angiogenesis in human umbilical cord vascular endothelial cells (HUVEC) [78, 79], and TRPC1 and TRPC4 are required for tubular formation in primary HUVEC in another report [80]. Additionally, hypoxia sensed by endothelial cells leads to growth factor production and vascular remodeling. TRPC3/TRPC4 heteromeric channels in endothelial cells and HEK293 cells are responsible for hypoxia-induced Ca^{2+} entry [81]. Ca^{2+} entry through TRPC channels plays an important role in agonist-induced vasoactivation. Endothelial cells in TRPC3$^{-/-}$ mesenteric arteries showed attenuated PE-stimulated vasoconstriction, impaired acetylcholine-induced nitro oxygen (NO) production, and increased vasodilatation [82, 83]. Similarly, in aortic endothelial cells of TRPC4$^{-/-}$ mice, acetylcholine-induced Ca^{2+} entry and vasodilatation are both reduced [74].

4.3 TRPCs in Lung Health and Disease

The lung is composed of multiple structural cell types including epithelial cells, airway smooth muscle, pulmonary vascular smooth muscle, and endothelial cells. Inflammatory lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), feature alterations in the morphology and function of structural cells. For example, there is epithelial hyperplasia and

development of an epithelial hypersecretory phenotype in asthma and chronic bronchitis and airway smooth muscle hypertrophy and hyperreactivity in asthmatics [84, 85]. Studies of expressions of TRPC channels suggest several TRPCs are highly expressed in different cell types and that their expression pattern levels are distinct [86, 87, 88], suggesting their unique functions in different cell types.

4.3.1 TRPCs in Lung Epithelial Cells

Little is known about TRPC expression in primary airway epithelial cells. TRPC1, TRPC4, and TRPC6 mRNA and TRPC6 protein are expressed in human bronchial epithelium and submucosal gland epithelium [86]. On the other hand, much more is known about the expression of TRPC channels in primary lung endothelial cells. There are several recent studies showing that TRPC1, TRPC3, TRPC4, TRPC6, and TRPC7 are expressed in either human or mouse pulmonary artery endothelial cells [57, 89].

Calcium ion influx through plasmalemmal calcium channels can impact the integrity of lung endothelial barrier and thus its permeability of fluid and protein. Store-operated Ca^{2+} entry increases lung endothelial permeability, both in vivo and in vitro [90]. It has been reported that store-operated calcium channels in culture pulmonary endothelium and caveolar fractions harvested from intact lung epithelium consist of TRPC1 and TRPC4 [91]. The interaction of TRPC4 and Orai1 is responsible for channel's calcium selectivity. Furthermore, thrombin-induced store-operated Ca^{2+} entry is reduced in lung endothelial cells isolated from TRPC4$^{-/-}$ mice [74]. However, in another study, activation of Ca^{2+} entry by OAG or thrombin in human pulmonary artery endothelium is reduced by treating the cells with siRNA against TRPC6 [75]. In concert with attenuated Ca^{2+} entry, RhoA activity, myosin light chain phosphorylation, actin stress fiber formation, and monolayer permeability are all decreased [75]. Ischemia-induced intracellular Ca^{2+} overload and subsequent increase of monolayer permeability are attenuated in endothelial cells isolated from TRPC6$^{-/-}$ mice. Thus, TRPC6$^{-/-}$ mice are protected from ischemia-induced increases in lung permeability and edema [92].

4.3.2 TRPCs in Airway Smooth Muscle Cells

Airway smooth muscles control the passage of air in airways. The dysfunction of airway smooth muscles is implicated in asthma. Excessive contraction of airway smooth muscle will cause airway narrowing, which is the primary mechanism of morbidity and mortality in asthma [93, 94]. Extracellular Ca^{2+} influx has been shown to play a critical role in smooth muscle contraction [95]. Multiple TRPC channels are expressed in smooth muscle cells, of which TRPC1, TRPC3, and TRPC6 have been shown to be expressed consistently across species [87, 96, 97].

TRPC3 is the major component of the native constitutively active nonselective cation channels in airway smooth muscle cells, of which the activity is increased in response to agonists [96]. They play an important role in various cellular responses including contraction, proliferation, migration, and gene expression in airway smooth muscle cells. TRPC3-encoded nonselective cation channels are also important for controlling the resting membrane potential and intracellular Ca^{2+} concentration in airway smooth muscle cells. Knocking down of TRPC3 results in a pronounced hyperpolarization by ~14 mV [96]. Moreover, *trpc3* gene silencing inhibits methacholine-, acetylcholine-, and tumor necrosis factor α (TNFα)-evoked $[Ca^{2+}]_i$, suggesting TRPC3 mediates agonist-induced $[Ca^{2+}]_i$ elevation in smooth muscle cells [98]. In reminiscent of these results, TRPC3 mRNA and protein level are significantly increased in airway smooth muscles following treatment with TNFα, an important asthma mediator [98]. These lines of evidence suggest that TRPC3 plays a fundamental role in smooth muscle physiology, and it is a prominent candidate for treatment of asthma.

4.4 Perspectives

In the past few years, TRPC channels have emerged as central players in various physiological processes. Mutations in these proteins are frequently associated with human diseases. As more information from the in vivo role of TRPC channels in animal models and clinical data from patients carrying mutations become available, our knowledge of the role of TRPC channels in disease pathogenesis will expand considerably. TRPC channels are expressed universally among most cell types. Studies from one system can be referenced to another. Further progress in mechanistic understanding of TRPC channels may help in identification of novel therapeutic targets.

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