Review

TRPC5 in cardiovascular diseases

Sheng-Li Du[1], Zeng-Qin Jia[2], Jiu-Chang Zhong[1,†,*], Le-Feng Wang[1,†,*]

[1] *Heart Center and Beijing Key Laboratory of Hypertension, Beijing Chaoyang Hospital, Capital Medical University, 100020 Beijing, P. R. China*

[2] *Miyun teaching hospital, Capital Medical University, 101500 Beijing, P. R. China*

*Correspondence: wlf20182021@126.com (Le-Feng Wang); jiuchangzhong@aliyun.com (Jiu-Chang Zhong)
†These authors contributed equally.

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Cardiovascular diseases (CVD), especially acute myocardial infarction, are the leading cause of death, morbidity and disability across the world, affecting millions of people each year. Atherosclerosis (AS) is the major cause of CVD, and is a chronic inflammation involving different cell types and various molecular mechanisms. Ca^{2+}dynamics of endothelial cells (ECs) and smooth muscle cells (SMCs) exert a significant influence on many aspects of CVD. Transient receptor potential channel 5 (TRPC5) is a member of the transient receptor potential (TRP) channels, which consists of a large number of nonselective cation channels with variable degrees of Ca^{2+}-permeability. As a Ca^{2+}-permeable cation channel, Human TRPC5 is expressed in a number of cell types, including ECs and muscle cells, as well as lungs and kidneys. TRPC5 is involved in renal, tumorous, neuronal and vascular diseases. In recent years, the roles of TRPC5 in CVD have been widely implicated in various disorders, such as AS, cardiac hypertrophy and blood pressure regulation. The TRPC5 mechanism of action may be associated with regulation of calcium homeostasis, oxidative stress and apoptosis. In this review, we highlight the significant roles of TRPC5 in the heart, and evaluate the potential of therapeutics targets which block TRPC5 for the treatment of CVD and related diseases.

Keywords

TRPC5; Atherosclerosis; Cardiovascular disease; Review

1. Introduction

CVD, especially coronary heart disease (CHD), is associated with high morbidity and mortality worldwide. Presently mortality and incidence rates among the elderly are increasing [1]. Although significant progress in the diagnosis and treatment of CVD has been made in recent years, the incidence rate and mortality rate remain high. Therefore, it is of high clinical significance that new therapeutic targets of CVD are explored. The intracellular Ca^{2+} ions play an essential role in cellular physiology, such as gene expression, cell cycle control, proliferation, autophagy, and apoptosis [2, 3]. Related to this, firstly observed in Drosophila, TRP channels are a group of non-voltage dependent calcium-permeable ion channels. To date, the TRP family stands for a large team of 28 cation channels fallen into six subfamilies in accordance with their structural homology: TRP canonical (TRPC), TRP melastin (TRPM), TRP vanniloid (TRPV), TRP ankyrin (TRPA), TRP mucolipin (TRPML), and TRP polycystin (TRPP), all of which permeate cations [4]. TRP can be activated by various stimuli, such as thermally-activated channels (TRPV, TRPM or TRPA) and TRPC activated by phospholipase C (PLC).

As the firstly encoded TRP gene family discovered in mammal, the canonical transient receptor potential channels (TRPCs) are the most leading non-voltage-gated, Ca^{2+}-permeable cation channels present in numerous cell types [5]. The TRPCs have been involved in neural development, brain function, and neurological disease [6]. To date seven TRPC isoforms (TRPC1 to 7) have been described in mammalian species, these have been fallen into four subfamilies on basis of their structural homology, functional similarities and direct known interactions: TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7 [7]. It should be noted that the TRPC4/5 subfamily sometimes included TRPC1. Despite as a pseudogene in humans, it is known that TRPC2 encodes functional channels in the majority of other mammals. Diacylglycerol formed by G protein-coupled receptors (GPCRs)/Gαq/PLC signaling activates TRPC3/6/7, while stretch or depletion of intracellular Ca^{2+} stores (store-operated Ca^{2+} entry, SOCE) activates TRPC1/4/5. It appears that nearly all of the isoforms (TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7) are upregulated during chronic cardiac disease in humans and in animal models [8, 9].

TRPC5 expression has been found in a lot of cell types with inheriting mechanosensitive Ca^{2+} influx, such as ECs, SMCs, cardiac myocytes and arterial baroreceptor neurons [10–13]. It can form channels on its own or assemble with TRPC4. The small ring in front of the disulphide bond in the extracellular region is the critical functional region of TRPC5 [14]. Studies have shown that TRPC5 channels are involved in different physiological and pathophysiological processes, including vascular smooth muscle, endothelial function, adiponectin regulation, oxidative stress, epilepsy, anxiety, pain and cardiac remodeling [13, 15–20]. The activation of TRPC5 can be made at the single-channel level if a certain threshold is reached by mechanical stress on the cell [21].

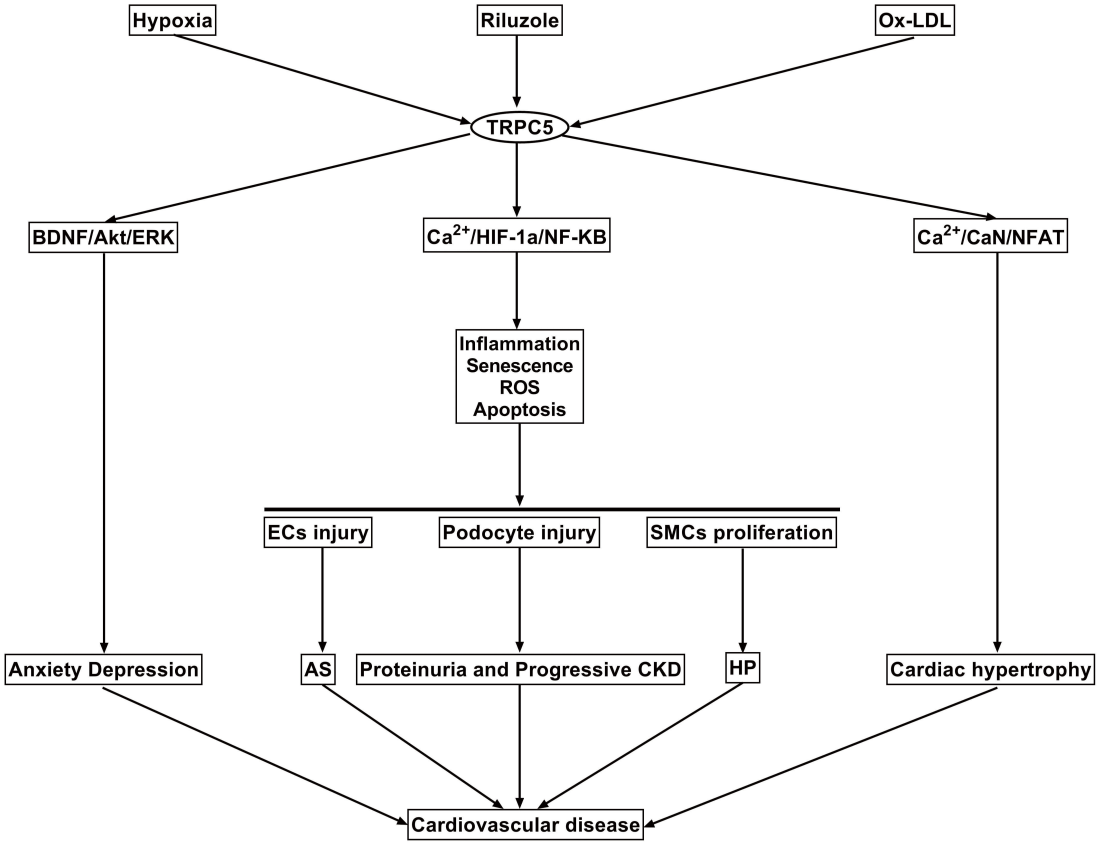

Fig. 1. The mechanisms of TRPC5 in the cardiovascular and related systems are outlined. First, under the stimulation of hypoxia, ox-LDL, or its activator, TRPC5 can cause endothelial cells damage and dysfunction, smooth muscle cell proliferation, atherosclerosis and high blood pressure by increasing inflammatory response, ROS, senescence and apoptosis. TRPC5 can also cause renal filtration barrier damage by injuring podocyte through the above mechanisms. Furthermore, TRPC5 can enhance the transcription of cardiac hypertrophy gene by regulating Ca^{2+}/CaN/NFAT, leading to cardiac hypertrophy. Finally, TRPC5 can also regulate BDNF and downstream signaling pathway to cause anxiety and depression and other emotional disorders. AS = atherosclerosis; BDNF = brain derived neurotrophic factor; EC = endothelial cell; ERK = extracellular regulated protein kinases; HIF-1α = hypoxia inducible factor-1α; HP = hypertension; NFAT = nuclear factor of activated T cells; NF-κB = nuclear transcription factor-κB; Ox-LDL = oxidized low-density lipoprotein; ROS = reactive oxygen species; SMC = smooth muscle cell.

2. TRPC5 and atherosclerosis

Atherosclerosis (AS) is one of the leading causes of coronary artery disease. EC injury is an essential basis of AS, whilst vascular SMCs (VSMCs), which play a critical role in maintaining blood vessel homeostasis, are also affected in this disease. Therefore the dysfunction of ECs and SMCs play essential roles in the pathogenesis of AS (Fig. 1). In response to injury, VSMCs proliferate, migrate, and release cytokines that can promote and increase inflammation. Interestingly the TRPC family, most commonly TRPC1, TRPC4 and TRPC5, are abundantly expressed in vascular SMCs. Fahy and colleagues (2008) confirmed that sphingosine 1-phosphate (S1P) can activate TRPC5, which is an endogenous signaling phospholipid participating in the migration of VSMCs. Therefore, activation of the TRPC5 channel can significantly promote the proliferation and migration of VSMCs [22]. Immunohistochemical techniques to detect the expression of TRPC5 in ECs and SMCs from murine carotid arteries have shown that blocking TRPC5 led to a great decrease in endothelium-dependent vasoconstriction [23].

Inflammation plays vital roles throughout the entire AS processes ranging from foam cell accumulation, fatty streak organization and fibrous plaque formation, through to acute plaque fissuring, rupture, and thrombosis. Numerous evidence sources define AS as a complicated and systemic pathology where hyperlipidaemia acts as an important element. The existence of inflammation is necessary for plaque evolution and destabilization and exerts a crucial effect on the pathogenesis and progression of coronary artery disease. Therefore it is of interest that TRPC5 is upregulated in inflammatory diseases. TRPC5 expression has been positively correlated with eosinophils, interleukin- 6 (IL-6), and phosphorylation levels of nuclear factor kappa-B (NF-κB). Blocking TRPC5 channels decreased store-operated calcium influx, IL-6 expression, and phosphorylation levels of NF-κB in blood eosinophils [24]. In contrast, another study investigating rheumatoid arthritis provided evidence of a potential role for TRPC5 as a negative regulator of inflammation as ac-

tivation of endogenous TRPC5 initiated a protective network against inflammatory insults. At the same time, it was noted that significant increases in the anti-inflammatory cytokine, interleukin-10 (IL-10), were present in TRPC5 knockout (KO) and antagonist-treated wild type (WT) mice [25]. The possible reason for this finding may be due to the unique formation mechanism of synovitis. Therefore, TRPC5 may play essential roles in regulating inflammatory balance *in vivo*.

Dyslipidemia is an independent risk factor for CVD. TRPC5 can promote cholestasis and dyslipidemia [26], while hypercholesterolemia can also positively activate TRPC5 and impair endothelial cell healing [27, 28]. TRPC5 channel protein has the characteristics of a lipid subtype receptor, which can recognize lysophosphatidylcholine as the main component of oxidation low lipoprotein (ox-LDL) and is activated by S1P in ox-LDL. The functioning mechanism of Statins, a commonly used lipid-lowering drug, is enabling delayed progression of AS by downregulating the TRPC5 protein expression. TRPC5 plays a vital role in the process of atherosclerosis mediated by hyperlipidemia, therefore blocking TRPC5 can delay the process of atherosclerosis.

Endothelial cell apoptosis is another critical step in the pathogenesis of AS [29]. Phospholipid scramblase 1 (PLSCR1) critically participates in phosphatidylserine (PS) externalization, a vital process in cell apoptosis. TRPC5 can mediate apoptosis by interacting with PLSCR1 and hypoxia-inducible factor-1α (HIF-1α) [30]. Inhibition of TRPC5 can significantly reduce apoptosis induced by hypoxia and ischemia [31]. Knockdown of TRPC5 can attenuate endothelial cell oxidative stress [32]. Therefore, TRPC5 can affect the process and progress of AS by regulating inflammation, aging, apoptosis, lipid metabolism and oxidative stress.

3. TRPC5 and myocardial ischemia

Most patients with acute myocardial infarction receive routine treatment with pharmacological reperfusion therapy and/or widening of the vessel with angioplasty. Nevertheless, critical injuries happen when the vulnerable myocardial tissue is reperfuses by oxygen-rich blood notably via mass manufacturing of mitochondrial reactive oxygen species. This situation is called ischemia/reperfusion (I/R) syndrome [33]. Apoptosis and tissue damage caused by ischemia-reperfusion are the leading causes of death in patients with fatal diseases such as myocardial infarction and stroke. According to the study, the growth in cytosolic Ca^{2+} is an important step in the initiation of myocardial cell apoptosis and necrosis in response to I/R [34, 35]. I/R induces an exacerbated store-operated calcium entry (SOCE) and upregulation of TRPC5, in addition to decreasing the amplitude of intracellular ($Ca^{2+}[Ca^{2+}]c_i$) transients and cardiomyocyte contractions in risk and remote zones [36]. Because TRPC5 KO mice suffered from less injury after I/R, better prognosis may be realized [30]. Urocortin-2 (Ucn-2) and Etidronate (Eti) are potent cardioprotectors against I/R injuries. Researchers have shown that addition of Ucn-2 or Eti at the beginning of reperfusion may attenuate I/R-induced adverse cardiac remodeling by maintaining calcium homeostasis and inhibiting expression of both TRPC5 and hypoxia-inducible factor-1α (HIF-1α) [31, 36].

Therapeutic angiogenesis promoting blood flow is essential while curing ischemia-related diseases [37–39], therefore TRPC5 may also have the potential to treat ischemic diseases. By activating HIF-1α-vascular endothelial growth factor (VEGF)/Twist and the nuclear factor of activated T cells 3 (NFATc3)-Angiopoietin 1 (ANGPT1) signaling pathway, TRPC5 promotes the migration and proliferation of vascular ECs and therefore increases angiogenesis [40–43]. Riluzole, an FDA-approved drug, can activateTRPC5 to promote ischemic tissue recovery. Unfortunately, most of the research on angiogenesis promotion is studied in tumour cells, therefore it is not clear how much effect it can have on normal tissues and cells. Consequently, when acute myocardial ischemia and hypoxia occur, whether the impact of TRPC5 on angiogenesis can improve myocardial injury has not yet been determined. Additionally, the angiogenic benefits of TRPC5 may not offset the inflammation and oxidative stress induced by TRPC5. Naturally this hypothesis needs to be confirmed by further experiments.

4. TRPC5 and heart failure

In early stage of heart failure (HF), changes in the expression and activity of Ca^{2+} related proteins, calcium homeostasis imbalanced are observed, which eventually results in cardiac dysfunction [44]. Various cationic channels permeating Ca^{2+} including TRPC make contributions to cardiomyopathies, cardiac fibrosis and cardiac remodelling [45]. Studies have demonstrated that TRPCs exert an essential effect on the pathological progress of cardiac hypertrophy through mediating ion channel activities and downstream signaling [10, 46]. Studies have confirmed that TRPC5 expression is upregulated in the human failing heart [47]. When TRPC5 expression is effectively reduced, early cardiac remodeling during I/R can effectively be avoided [36], therefore blocking TRPC5 activity to improve cardiac structure and function after myocardial ischemia is an effective way of treating CVD [9] (Fig. 1). However, another research found that hypertrophic gene expression can't be induced sufficiently by transient activation of nuclear factor of activated T cells (NFAT) mediated by TRPC5-dependent Ca^{2+} entry. Just the opposite occurs, TRPC5 functionally couples with endothelial nitric oxide synthase (eNOS), and activation of TRPC5-mediated nitric oxide (NO) signaling negatively regulates hypertrophic responses by suppressing TRPC3/C6-mediated Na^{+}/Ca^{2+} influx and sustained Ca^{2+}/NFAT activation [48]. However, cardiac hypertrophy pathological mechanisms are very complex, and include inflammation, oxidative stress, aging, apoptosis, and calcium homeostasis imbalance [49]. TRPC5 may be a cause of cardiac hypertrophy through the above mechanism, but also partially offset cardiac hypertrophy through eNOS. Therefore, further researches are needed

to confirm the role of TRPC5 channels in cardiac hypertrophy and HF.

5. TRPC5 and hypertension

Recently, a lot of researches have paid attention to the relationships between initial hypertension and TRPCs [50]. Members of the TRPC subfamily are involved in primary hypertension due to the Ca^{2+} entry pathways participating in both pulmonary and primary hypertension, as well as them boosting vascular disease in hypertension [51]. A key signaling mechanism stimulating the calcium-dependent release of several endothelium-derived vasoconstrictive agents, including endothelin, urotensin, and epoxyeicosatrienoic acids is underlaid by the TRPC5-mediated calcium influx, which contribute towards the growth of hypertension [52–54]. Moreover, previous studies have convincingly shown that TRPC5 promotes vascular smooth muscle cell proliferation and increases oxidative stress, which may in turn induce the occurrence of hypertension [32]. Animal experiments showed that TRPC5 expression was positively correlated with systolic blood pressure (SBP) and diastolic blood pressure (DBP). TRPC5 expression was also significantly increased in patients with primary hypertension and also in spontaneously hypertensive rats [55–58]. Obstructive sleep apnea-hypopnea syndrome (OSAHS) is also identified as an independent risk factor of cardiovascular disease. The expression of TRPC5 has been shown be be significantly increased in OSAHS patients by comparing with the control group ($P < 0.05$) [59]. When combined, this research suggests that TRPC5 may be a biomarker of elevated blood pressure.

As a polymodal channel enriched in neuronal cells, TRPC5 also localizes to the aortic baroreceptor termini, sensory neuronal termini for blood pressure detection [12]. In addition, TRPC5 can be directly activated by membrane stretch [21], which is independent of phospholipase C. In TRPC5 knockout mice, the pressure-induced action potential firings in the afferent nerve and the baroreflex-mediated heart rate reduction were attenuated. Telemetric measurements of blood pressure demonstrate that these TRPC5 knockout mice also display severe daily blood pressure fluctuations [60]. This suggests that TRPC5 channels stand for a core pressure transducer in the baroreceptors and exert a primary role in keeping blood pressure stable.

Therefore, in relation to the aspect of prevention and treatment of hypertension, could blocking TRPC5 reduce blood pressure and offset the blood pressure fluctuation caused by it? We look forward to further support from future relevant research.

6. TRPC5 and arrhythmia

Intracellular calcium ion (Ca^{2+}) is critical for regulation of a variety of fundamental cellular processes, as dysregulation of intracellular calcium homeostasis can lead to pathological outcomes such as arrhythmias and cardiac hypertrophy. The TRPC channels exert a significant effect on regulating calcium homeostasis in the body. Besides this work, studies have also shown that TRPC channels can also influence the occurrence and development of atrial fibrillation (AF) by regulating cardiac fibroblast functions, thus TRPCs may affect the cardiac electrical activity in a variety of ways. Several experiments have shed light on TRPC-regulated Ca^{2+} entry in arrhythmia [61, 62]. However, these studies are mainly about other subtypes within the TRPC family (such as TRPC3, TRPC6), with only one observational study on TRPC5. This study showed that TRPC5 gene expression was significantly increased in leukocytes from patients with nonvalvular AF [63]. Whilst one might suggest that the best tissue or cell to study AF would be the left atrium, researches have already indicated that inflammation and oxidative stress participate in the occurrence and development of AF [64–66]. As a result, the white blood cells in peripheral blood may still reflect the degree of inflammation in patients with AF to a certain extent [67, 68].

Additionally, oxidizing agents can directly activate TRPC5 channels through cysteine modification [69]. This implies that TRPC5 may be a useful target for the prevention of AF. But more researches on TRCP5 in arrhythmias are needed in the future.

7. TRPC5 and emotion regulation

According to various researches, CVD is closely associated with mental health disorders. As an independent risk factor of CVD, emotional disorders play vital roles in the occurrence and development of CVD. The effective control of depression in patients with CVD, for example, has a potential auxiliary effect on the prevention of various types of CVD, such as coronary heart disease and heart failure. TRPC5 is highly expressed in the hippocampus and amygdala, which can regulate anxiety. Within the nervous system, one of the most studied fields relating to TRPC5 is its anti-anxiety and anti-depression effects. The evidence for this effect is obtained from studies using transgenic mouse models and pharmacological modulators. For example, M084, a TRPC5 inhibitor, plays a rapid anti-depressant and anti-anxiety role by increasing the expression of brain-derived neurotrophic factor (BDNF) mRNA and protein in the prefrontal cortex, as well as increasing the phosphorylation level of protein kinase B (Akt) and extracellular regulated protein kinases (ERK) [70]. Following TRPC5 molecule blocker treatment in experimental mice, behavioural evaluation showed that the inhibitor had the potential for anti-anxiety and anti-depression effects [17, 71] (Fig. 1). This suggests that TRPC5 has potential for not only treating nervous system diseases, but also as an additional treatment for CVD.

8. TRPC5 and renal protection

Renal barrier dysfunction is a risk factor for CVD and kidney disease. In the treatment of coronary heart disease, drugs and devices inevitably produce different degrees of re-

nal damage. Acute renal injury caused by the use of contrast medium in interventional surgery, i.e. contrast medium nephropathy, is a common clinical focus in both heart and kidney disease. TRPC5 is also involved in kidney disease [72]. Podocytes are special cells that form the filtration membrane of kidney. TRPC5 channels are expressed in podocytes and are involved in the regulation of cell migration and actin remodeling stimulated by angiotensin [73] (Fig. 1). Schaldecker and colleagues confirmed that TRPC5 is the main pathway for lipopolysaccharide (LPS) induced proteinuria. Application of TRPC5 inhibitors can block LPS induced proteinuria, and protect renal podocytes from LPS induced microfilament remodeling [74]. Yiming Zhou (2017) applied a TRPC5 inhibitor to treat rats with glomerulonephritis, and achieved the same results. AC1903, a small molecule inhibitor of TRPC5 channel, inhibited severe proteinuria in focal segmental glomerular sclerosis (FSGS) transgenic rats and prevented podocyte loss. AC1903 also had a therapeutic effect on hypertensive proteinuria in rats. These trials suggest that TRPC5 inhibitors may provide significant value during the treatment of hypertensive renal injury [75]. GFB-8438, another more recent TRPC5 inhibitor, significantly reduced urinary total protein and albumin concentrations and protected podocytes from protamine sulphate (PS) injury [76]. Hypertension acts as an ordinary complication among hemodialysis patients during erythropoietin (EPO) treatment. EPO increased the stability of TRPC5 mRNA and the concentrations of TRPC5 channel protein. Additionally, TRPC5 gene knockout can reduce the generation of reactive oxygen species in endothelial cells induced by EPO [32]. This indicated that upregulated functional TRPC5 gene may act as one of the causes of EPO-induced hypertension among patients with chronic kidney disease. Therefore, inhibition of TRPC5 may protect renal filtration barrier from acute reversible injury and has a great potential in the field of heart and kidney treatment.

In contrast to other studies, the protective role of blocking TRPC5 in progressive kidney disease was not supported in transgenic mice overexpressing either WT TRPC5 or a dominant-negative TRPC5 mutant [77]. No differences in LPS-induced kidney damage were observed among the different groups, and there is no effect of the treatment with the inhibitor ML204 on proteinuria in LPS-challenged animals. And treatment with the TRPC5 activator (-)EA exerted no bad influence on proteinuria in mice. Nevertheless, due to the poor stability of (-)EA in plasma [78], it is still controversial as to whether the plasma concentration of (-)EA can activate the TRPC5 channel and lead to renal injury. In addition, as van der Wijst and Bindels [79] mentioned, the dosage and administration scheme of ML204 used in the above studies are different, which may lead to differential results. In order to discriminate and conclude potential actions, the roles of TRPC5 in renal diseases shall be elucidated by further studies.

9. Challenges for clinical use

Over the last 20 years, research into TRPC5 has been limited to relatively basic experiments and clinical translational research is proceeding very slowly. This may be due to the following reasons: Firstly, TRPC5 channels are widely distributed around the human body, and inhibition of TRPC5 may lead to various complications. Since all TRPC channels, including TRPC5, are commonly distributed throughout the body and can also regulate a variety of cellular functions, the adverse effects of nonselective inhibition, such as significantly increased bleeding time [80] and cognitive impairment [81], could become a major obstacle to the use of TRPC blockers. Therefore, due to safety reasons, clinical translation of TRPC5 inhibitors have progressed slowly. Secondly, current research on TRPC5 have mainly focused on cell lines, and gene knockout or overexpression models *in vivo*. There is a gap between these studies and those needed in humans. Prior to clinical drug development, it is necessary to demonstrate how TRPC5 is altered in human biopsy samples. Thirdly, from the perspective of the current clinical development history of drugs targeting ion channels, such as Bolapamil, lidocaine and diazepam, early research results were restricted because of the shortage of specificity and significant off-target effects. This also restricted their clinical applicability [82]. Consequently researchers need to develop drugs that are more specific and have fewer off-target effects. Fourthly, the specific roles and mechanisms of TRPC5 in heart disease are still unclear, and further researches shall be made to illustrate the molecular mechanisms (including key regulatory sites and signaling pathways) of TRPC5 channels involved in cardiovascular disease. This will help to design drugs specifically targeting the TRPC5 channels. Finally, TRPC5 channels are abundantly expressed in the brain and exert a significant effect on signal transmission within the nervous system. Therefore, TRPC5 inhibitors that cannot pass the blood-brain barrier should be developed, thus ensuring they can be safely used in clinical practice.

Translational research needs to be combined with research in clinical and pharmaceutical settings in addition to other fields. Therefore, we believe that the future research direction of TRPC5 is as follows: (1) Search for highly specific inhibitors to reduce the incidence of side effects. (2) Validate the results in more animal models, preferably those most similar to humans. (3) Clarify the roles and molecular mechanisms of TRPC5 in cardiovascular diseases. (4) Regulate molecules in the upstream and downstream signaling pathways of the TRPC5 channel.

Currently, several small molecular compounds have been used in basic experiments, such as HC-070 [17], ML204 [83], AC1903 [75], in addition to others. Laboratory studies of these smaller molecular compounds may provide valuable insights into the roles of TRPC5 within both cells and animal disease models. This is beneficial for the development of new drugs targeting TRPC5. Also, to conveniently detect the expression of TRPC5 under different conditions, researchers

Table 1. Different roles of TRPC5 in cardiovascular disease.

Role	Reference	Object	Outcome	Effects of blocking TRPC5
inflammation	[24]	patient	TRPC5 expression was positively correlated with eosinophils, IL-6, and phosphorylation levels of NF-κB.	anti-inflammatory
VSMC	[22]	animal cell	TRPC5 mediates VSMC migration.	anti-VSMC migration
dyslipidemia	[25]	animal	TRPC5 contributes to the development of cholestasis and dyslipidemia.	regulate blood lipids
apoptosis	[30, 31]	animal cell	TRPC5-PLSCR1 is a signaling complex mediating PS externalization and apoptosis, decreased TRPC5 protein may resist cell apoptosis injured by $CoCl_2$.	anti-apoptosis
oxidative stress	[32]	patients cell	Knockdown of TRPC5 alleviated EPO-induced reactive oxygen species generation in endothelial cells.	Antioxidant stress
I/R injury	[30, 36]	animal cell	Reduced I/R-induced adverse cardiac remodeling was associated with decreased TRPC5 expression.	Reduce I/R injury
angiogenesis	[40–43]	animal cell	TRPC5 mediated HIF-1α expression, and is involved in endothelial cell sprouting, angiogenesis.	Reduce angiogenesis, which is detrimental to ischemic disease
cardiac hypertrophy	[36]	animal cell	Reduced I/R-induced adverse cardiac remodeling was associated with decreased TRPC5 expression.	Anti-cardiac hypertrophy
blood pressure	[60]	animal	TRPC5 knockout mice display severe daily blood pressure fluctuation, suggest TRPC5 channels stand for a core pressure transducer in the baroreceptors and exert a significant effect on keeping blood pressure stable.	Display severe daily blood pressure fluctuation
cardiac rhythm	[63]	patient	TRPC5 gene expressions in NVAF patients had a marked increasing.	May be beneficial to the treatment of NVAF
emotion	[70, 71]	animal	$TRPC5^{-/-}$ mice exhibit diminished innate fear levels in response to innately aversive stimuli. Blocking TRPC5 exerts rapid anti-depressant and anxiolytic-like effects.	anti-anxiety, anti-depression
kidney	[74, 75]	animal	TRPC5 mediates filtration barrier injury. genetic deletion or pharmacologic inhibition of TRPC5 protected mice from albuminuria and podocyte loss.	Protect kidney podocyte, reduce albuminuria

EPO = erythropoietin; HIF-1α = hypoxia-inducible factor 1 alpha; I/R = Ischemia-reperfusion; NVAF = Non-valvular atrial fibrillation; PLSCR1 = Phospholipid scramblase 1; $TRPC5^{-/-}$ = TRPC5 gene double knockout; VSMC = Vascular smooth muscle cells; NF-κB = nuclear factor kappa-B.

have synthesized a TRPC5 PET radiotracer, [11C]HC608, to quantify TRPC5 expression changes in the brain [84]. Unfortunately, to dtae, there have been no similar studies in the heart. These approaches would benefit our understanding of the roles of TRPC5 in the heart, especially if PET-CT and tracers were used for quantification of TRPC5 expression in cardiovascular diseases.

10. Summary

We have focused on the critical effect of TRPC5 in multi-organ areas, especially within the cardiovascular and AS fields. By regulating intracellular Ca^{2+} homeostasis, oxidative stress, and apoptosis, TRPC5 participates in the migration and proliferation of vascular smooth muscle cells, endothelial cell injury and dysfunction, lipid deposition, and cardiac hypertrophy. Blocking TRPC5 channels can inhibit the atherosclerotic plaque formation, reduce expression of cardiac hypertrophy associated genes, maintain stability of cardiac electrical activity, and thus play anti-AS, anti-cardiac hypertrophy and anti-arrhythmia roles. In addition, blocking TRPC5 can prevent depression and anxiety, improve renal function, regulate blood lipids, and thus play a synergistic role in improving the prognosis of CVD patients. However, activation of TRPC5 channels can also regulate blood pressure, promote angiogenesis, and has the potential to stabilize blood pressure as well as resist ischemia (See Table 1). There are also conflicting findings regarding TRPC5 in inflammation and renal therapy. Therefore, in order to explain these controversies and develop clinical drugs with high specificity which produce few side effects, the relevant signaling pathways and molecular mechanisms should be confirmed by further researches. In general, the TRPC5 channel should still be considered as a promising therapeutic target for regulating heart disease.

Author contributions

Du Sheng-li and Jia Zeng-qin conducted literature search and wrote the paper. Wang le-feng and Zhong Jiu-chang reviewed and edited the manuscript.

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Conflict of interest

The author declares no conflicts of interests.

References

[1] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, *et al.* Heart Disease and Stroke Statistics-2018 Update: a Report from the American Heart Association. Circulation. 2019; 137: e67-e492.

[2] Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signalling. Nature Reviews Molecular Cell Biology. 2000; 1: 11-21.

[3] Cui C, Merritt R, Fu L, Pan Z. Targeting calcium signaling in cancer therapy. Acta Pharmaceutica Sinica B. 2017; 7: 3-17.

[4] Montell C. Drosophila TRP channels. Pflugers Archiv : European Journal of Physiology. 2006; 451: 19-28.

[5] Zhu X, Chu PB, Peyton M, Birnbaumer L. Molecular cloning of a widely expressed human homologue for the Drosophila trp gene. FEBS Letters. 1995; 373: 193-198.

[6] Selvaraj S, Sun Y, Singh BB. TRPC channels and their implication in neurological diseases. CNS & Neurological Disorders Drug Targets. 2010; 9: 94-104.

[7] Birnbaumer L. The TRPC Class of Ion Channels: a Critical Review of their Roles in Slow, Sustained Increases in Intracellular Ca^{2+} Concentrations. Annual Review of Pharmacology and Toxicology. 2009; 49: 395-426.

[8] Kirschmer N, Bandleon S, von Ehrlich-Treuenstätt V, Hartmann S, Schaaf A, Lamprecht AK, *et al.* TRPC4α and TRPC4β Similarly Affect Neonatal Cardiomyocyte Survival during Chronic GPCR Stimulation. PloS One. 2016; 11: e0168446.

[9] Makarewich CA, Zhang H, Davis J, Correll RN, Trappanese DM, Hoffman NE, *et al.* Transient Receptor Potential Channels Contribute to Pathological Structural and Functional Remodeling after Myocardial Infarction. Circulation Research. 2014; 115: 567-580.

[10] Bush EW, Hood DB, Papst PJ, Chapo JA, Minobe W, Bristow MR, *et al.* Canonical Transient Receptor Potential Channels Promote Cardiomyocyte Hypertrophy through Activation of Calcineurin Signaling. Journal of Biological Chemistry. 2006; 281: 33487-33496.

[11] Flemming PK, Dedman AM, Xu S, Li J, Zeng F, Naylor J, *et al.* Sensing of lysophospholipids by TRPC5 calcium channel. Journal of Biological Chemistry. 2006; 281: 4977-4982.

[12] Glazebrook PA, Schilling WP, Kunze DL. TRPC channels as signal transducers. PflüGers Archiv - European Journal of Physiology. 2005; 451: 125-130.

[13] Yip H, Chan W, Leung P, Kwan H, Liu C, Huang Y, *et al.* Expression of TRPC homologs in endothelial cells and smooth muscle layers of human arteries. Histochemistry and Cell Biology. 2004; 122: 553-561.

[14] Duan J, Li J, Chen GL, Ge Y, Liu J, Xie K, *et al.* Cryo-EM structure of TRPC5 at 2.8-Å resolution reveals unique and conserved structural elements essential for channel function. Science Advances. 2019; 5: eaaw7935.

[15] Camacho Londoño JE, Tian Q, Hammer K, Schröder L, Camacho Londoño J, Reil JC, *et al.* A background Ca^{2+} entry pathway mediated by TRPC1/TRPC4 is critical for development of pathological cardiac remodelling. European Heart Journal. 2016; 36: 2257-2266.

[16] Gaunt HJ, Vasudev NS, Beech DJ. Transient receptor potential canonical 4 and 5 proteins as targets in cancer therapeutics. European Biophysics Journal. 2017; 45: 611-620.

[17] Just S, Chenard BL, Ceci A, Strassmaier T, Chong JA, Blair NT, *et al.* Treatment with HC-070, a potent inhibitor of TRPC4 and TRPC5, leads to anxiolytic and antidepressant effects in mice. PloS One. 2018; 13: e0191225.

[18] Miller BA. The role of TRP channels in oxidative stress-induced cell death. Journal of Membrane Biology. 2006; 209: 31-41.

[19] Sukumar P, Sedo A, Li J, Wilson LA, O'Regan D, Lippiat JD, *et al.* Constitutively active TRPC channels of adipocytes confer a mechanism for sensing dietary fatty acids and regulating adiponectin. Circulation Research. 2012; 111: 191-200.

[20] Westlund KN, Zhang LP, Ma F, Nesemeier R, Ruiz JC, Ostertag EM, *et al.* A rat knockout model implicates TRPC4 in visceral pain sensation. Neuroscience. 2014; 262: 165-175.

[21] Shen B, Wong C, Lau O, Woo T, Bai S, Huang Y, *et al.* Plasma membrane mechanical stress activates TRPC5 channels. PloS One. 2015; 10: e0122227.

[22] Fahy S. Sphingosine-1-phosphate activation of TRPC5 in vascular smooth muscle cells. Bioscience Horizons. 2008; 1: 92-97.

[23] Liang C, Zhang Y, Zhuo D, Lo C, Yu L, Lau C, *et al.* Endothelial cell transient receptor potential channel C5 (TRPC5) is essential for endothelium-dependent contraction in mouse carotid arteries. Biochemical Pharmacology. 2019; 159: 11-24.

[24] Fu Z, Gu L, Li N, Ma Z, Ling M, Wang Y. Upregulated TRPC5 plays an important role in development of nasal polyps by activating eosinophilic inflammation and NF-κB signaling pathways. International Journal of Clinical and Experimental Pathology. 2018; 11: 1935-1945.

[25] Alawi KM, Russell FA, Aubdool AA, Srivastava S, Riffo-Vasquez Y, Baldissera L, *et al.* Transient receptor potential canonical 5 (TRPC5) protects against pain and vascular inflammation in arthritis and joint inflammation. Annals of the Rheumatic Diseases. 2017; 76: 252-260.

[26] Alawi KM, Tandio D, Xu J, Thakore P, Papacleovoulou G, Fernandes ES, *et al.* Transient receptor potential canonical 5 channels plays an essential role in hepatic dyslipidemia associated with cholestasis. Scientific Reports. 2017; 7: 2338.

[27] Chaudhuri P, Rosenbaum MA, Sinharoy P, Damron DS, Birnbaumer L, Graham LM. Membrane translocation of TRPC6 channels and endothelial migration are regulated by calmodulin and PI3 kinase activation. Proceedings of the National Academy of Sciences. 2016; 113: 2110-2115.

[28] Rosenbaum MA, Chaudhuri P, Graham LM. Hypercholesterolemia inhibits re-endothelialization of arterial injuries by TRPC channel activation. Journal of Vascular Surgery. 2016; 62: 1040-1047.e2.

[29] Choy JC, Granville DJ, Hunt DWC, McManus BM. Endothelial cell apoptosis: biochemical characteristics and potential implications for atherosclerosis. Journal of Molecular and Cellular Cardiology. 2001; 33: 1673-1690.

[30] Guo J, Li J, Xia L, Wang Y, Zhu J, Du J, *et al.* Transient Receptor Potential Canonical 5-Scramblase Signaling Complex Mediates Neuronal Phosphatidylserine Externalization and Apoptosis. Cells. 2020; 9: 547.

[31] Li K, Li W, Yin H, Cheong YK, Ren G, Yang Z. Pretreatment-Etidronate Alleviates CoCl(2) Induced-SH-SY5Y Cell Apoptosis via Decreased HIF-1α and TRPC5 Channel Proteins. Neurochemical Research. 2019; 44: 428-440.

[32] Liu Y, Xu Y, Thilo F, Friis UG, Jensen BL, Scholze A, *et al.* Erythropoietin Increases Expression and Function of Transient Receptor Potential Canonical 5 Channels. Hypertension. 2011; 58: 317-324.

[33] Hausenloy DJ, Botker HE, Engstrom T, Erlinge D, Heusch G, Ibanez B, *et al.* Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. European Heart Journal. 2016; 36: ehw145.

[34] Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu S. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. American Journal of Physiology. Cell Physiology. 2004; 287: C817-C833.

[35] Carafoli E. Calcium signaling: a tale for all seasons. Proceedings of the National Academy of Sciences. 2002; 99: 1115-1122.

[36] Domínguez-Rodríguez A, Mayoral-Gonzalez I, Avila-Medina J, de Rojas-de Pedro ES, Calderón-Sánchez E, Díaz I, *et al.* Urocortin-2 prevents dysregulation of Ca^{2+} homeostasis and improves early cardiac remodeling after ischemia and reperfusion. Frontiers in Physiology. 2018; 9: 813.

[37] Albrecht-Schgoer K, Barthelmes J, Schgoer W, Theurl M, Nardin I, Lener D, *et al.* Nanoparticular delivery system for a secretoneurin derivative induces angiogenesis in a hind limb ischemia model. Journal of Controlled Release. 2017; 250: 1-8.
[38] Suzuki J, Shimamura M, Suda H, Wakayama K, Kumagai H, Ikeda Y, *et al.* Current therapies and investigational drugs for peripheral arterial disease. Hypertension Research. 2016; 39: 183-191.
[39] Ylä-Herttuala S, Bridges C, Katz MG, Korpisalo P. Angiogenic gene therapy in cardiovascular diseases: dream or vision? European Heart Journal. 2018; 38: 1365-1371.
[40] Antigny F, Girardin N, Frieden M. Transient receptor potential canonical channels are required for in vitro endothelial tube formation. Journal of Biological Chemistry. 2012; 287: 5917-5927.
[41] Chen Z, Zhu Y, Dong Y, Zhang P, Han X, Jin J, *et al.* Overexpression of TrpC5 promotes tumor metastasis via the HIF-1α-Twist signaling pathway in colon cancer. Clinical Science. 2017; 131: 2439-2450.
[42] Zhu Y, Gao M, Zhou T, Xie M, Mao A, Feng L, *et al.* The TRPC5 channel regulates angiogenesis and promotes recovery from ischemic injury in mice. Journal of Biological Chemistry. 2019; 294: 28-37.
[43] Zhu Y, Pan Q, Meng H, Jiang Y, Mao A, Wang T, *et al.* Enhancement of vascular endothelial growth factor release in long-term drug-treated breast cancer via transient receptor potential channel 5-Ca$^{(2+)}$-hypoxia-inducible factor 1α pathway. Pharmacological Research. 2015; 93: 36-42.
[44] Kho C, Lee A, Hajjar RJ. Altered sarcoplasmic reticulum calcium cycling–targets for heart failure therapy. Nature Reviews. Cardiology. 2013; 9: 717-733.
[45] Smani T, Shapovalov G, Skryma R, Prevarskaya N, Rosado JA. Functional and physiopathological implications of TRP channels. Biochimica Et Biophysica Acta. 2015; 1853: 1772-1782.
[46] Nakayama H, Wilkin BJ, Bodi I, Molkentin JD. Calcineurin-dependent cardiomyopathy is activated by TRPC in the adult mouse heart. FASEB Journal. 2006; 20: 1660-1670.
[47] Dragún M, Gažová A, Kyselovič J, Hulman M, Máťuš M. TRP Channels Expression Profile in Human End-Stage Heart Failure. Medicina. 2019; 55: 380.
[48] Sunggip C, Shimoda K, Oda S, Tanaka T, Nishiyama K, Mangmool S, *et al.* TRPC5-eNOS Axis Negatively Regulates ATP-Induced Cardiomyocyte Hypertrophy. Frontiers in Pharmacology. 2019; 9: 523.
[49] Samak M, Fatullayev J, Sabashnikov A, Zeriouh M, Schmack B, Farag M, *et al.* Cardiac Hypertrophy: an Introduction to Molecular and Cellular Basis. Medical Science Monitor Basic Research. 2016; 22: 75-79.
[50] Fuchs B, Dietrich A, Gudermann T, Kalwa H, Grimminger F, Weissmann N. The Role of Classical Transient Receptor Potential Channels in the Regulation of Hypoxic Pulmonary Vasoconstriction. Advances in Experimental Medicine and Biology. 2010; 71: 187-200.
[51] Firth AL, Remillard CV, Yuan JX. TRP channels in hypertension. Biochimica Et Biophysica Acta. 2007; 1772: 895-906.
[52] Fleming I, Busse R. Endothelium-Derived Epoxyeicosatrienoic Acids and Vascular Function. Hypertension. 2006; 47: 629-633.
[53] Thijssen DHJ, Rongen GA, Smits P, Hopman MTE. Physical (in)activity and endothelium-derived constricting factors: overlooked adaptations. Journal of Physiology. 2008; 586: 319-324.
[54] Watanabe T, Kanome T, Miyazaki A, Katagiri T. Human urotensin II as a link between hypertension and coronary artery disease. Hypertension Research : Official Journal of the Japanese Society of Hypertension. 2006; 29: 375-387.
[55] Chen X, Yang D, Ma S, He H, Luo Z, Feng X, *et al.* Increased rhythmicity in hypertensive arterial smooth muscle is linked to transient receptor potential canonical channels. Journal of Cellular and Molecular Medicine. 2010; 14: 2483-2494.
[56] Liu D, Scholze A, Zhu Z, Krueger K, Thilo F, Burkert A, *et al.* Transient receptor potential channels in essential hypertension. Journal of Hypertension. 2006; 24: 1105-1114.
[57] Liu DY, Thilo F, Scholze A, Wittstock A, Zhao ZG, Harteneck C, *et al.* Increased store-operated and 1-oleoyl-2-acetyl-sn-glycerol-induced calcium influx in monocytes is mediated by transient receptor potential canonical channels in human essential hypertension. Journal of Hypertension. 2007; 25: 799-808.
[58] Liu F, Ma Z, Li D, Feng J, Zhang K, Wang R, *et al.* Differential expression of TRPC channels in the left ventricle of spontaneously hypertensive rats. Molecular Biology Reports. 2010; 37: 2645-2651.
[59] Wen W, Yao Q, Chen Y, Li Z, Maitikuerban B, Zhang Y, *et al.* Transient receptor potential canonical 5 channel is involved in the cardiac damage related to obstructive sleep apnea-hypopnea syndrome in rats. Annals of Palliative Medicine. 2020; 9: 895-902.
[60] Lau O, Shen B, Wong C, Tjong Y, Lo C, Wang H, *et al.* TRPC5 channels participate in pressure-sensing in aortic baroreceptors. Nature Communications. 2016; 7: 11947.
[61] Harada M, Luo X, Qi XY, Tadevosyan A, Maguy A, Ordog B, *et al.* Transient Receptor Potential Canonical-3 Channel–Dependent Fibroblast Regulation in Atrial Fibrillation. Circulation. 2012; 126: 2051-2064.
[62] Ju Y, Lee BH, Trajanovska S, Hao G, Allen DG, Lei M, *et al.* The involvement of TRPC3 channels in sinoatrial arrhythmias. Frontiers in Physiology. 2015; 6: 86.
[63] Düzen IV, Yavuz F, Vuruskan E, Saracoglu E, Poyraz F, Göksülük H, *et al.* Leukocyte TRP channel gene expressions in patients with non-valvular atrial fibrillation. Scientific Reports. 2017; 7: 9272.
[64] Gutierrez A, Van Wagoner DR. Oxidant and Inflammatory Mechanisms and Targeted Therapy in Atrial Fibrillation. Journal of Cardiovascular Pharmacology. 2015; 66: 523-529.
[65] Patel P, Dokainish H, Tsai P, Lakkis N. Update on the Association of Inflammation and Atrial Fibrillation. Journal of Cardiovascular Electrophysiology. 2010; 21: 1064-1070.
[66] Shimano M, Shibata R, Inden Y, Yoshida N, Uchikawa T, Tsuji Y, *et al.* Reactive oxidative metabolites are associated with atrial conduction disturbance in patients with atrial fibrillation. Heart Rhythm. 2009; 6: 935-940.
[67] Gurses KM, Kocyigit D, Yalcin MU, Canpinar H, Yorgun H, Sahiner ML, *et al.* Monocyte Toll-Like Receptor Expression in Patients with Atrial Fibrillation. American Journal of Cardiology. 2016; 117: 1463-1467.
[68] Raman K, Aeschbacher S, Bossard M, Hochgruber T, Zimmermann AJ, Kaufmann BA, *et al.* Whole Blood Gene Expression Differentiates between Atrial Fibrillation and Sinus Rhythm after Cardioversion. PloS One. 2017; 11: e0157550.
[69] Ogawa N, Kurokawa T, Mori Y. Sensing of redox status by TRP channels. Cell Calcium. 2016; 60: 115-122.
[70] Yang L, Jiang F, Wu G, Deng K, Wen M, Zhou X, *et al.* Acute Treatment with a Novel TRPC4/C5 Channel Inhibitor Produces Antidepressant and Anxiolytic-Like Effects in Mice. PloS One. 2016; 10: e0136255.
[71] Riccio A, Li Y, Moon J, Kim K, Smith KS, Rudolph U, *et al.* Essential Role for TRPC5 in Amygdala Function and Fear-Related Behavior. Cell. 2009; 137: 761-772.
[72] Hall G, Wang L, Spurney RF. TRPC Channels in Proteinuric Kidney Diseases. Cells. 2019; 9: 44.
[73] Tian D, Jacobo SMP, Billing D, Rozkalne A, Gage SD, Anagnostou T, *et al.* Antagonistic regulation of actin dynamics and cell motility by TRPC5 and TRPC6 channels. Science Signaling. 2011; 3: ra77.
[74] Schaldecker T, Kim S, Tarabanis C, Tian D, Hakroush S, Castonguay P, *et al.* Inhibition of the TRPC5 ion channel protects the kidney filter. Journal of Clinical Investigation. 2013; 123: 5298-5309.
[75] Zhou Y, Castonguay P, Sidhom E, Clark AR, Dvela-Levitt M, Kim S, *et al.* A small-molecule inhibitor of TRPC5 ion channels suppresses progressive kidney disease in animal models. Science (New York, N.Y.). 2018; 358: 1332-1336.

[76] Yu M, Ledeboer MW, Daniels M, Malojcic G, Tibbitts TT, Coeffet-Le Gal M, *et al.* Discovery of a Potent and Selective TRPC5 Inhibitor, Efficacious in a Focal Segmental Glomerulosclerosis Model. ACS Medicinal Chemistry Letters. 2019; 10: 1579-1585.
[77] Wang X, Dande RR, Yu H, Samelko B, Miller RE, Altintas MM, *et al.* TRPC5 does not Cause or Aggravate Glomerular Disease. Journal of the American Society of Nephrology. 2018; 29: 409-415.
[78] Carson C, Raman P, Tullai J, Xu L, Henault M, Thomas E, *et al.* Englerin a Agonizes the TRPC4/C5 Cation Channels to Inhibit Tumor Cell Line Proliferation. PLoS ONE. 2015; 10: e0127498.
[79] van der Wijst J, Bindels RJM. Renal physiology: TRPC5 inhibition to treat progressive kidney disease. Nature Reviews. Nephrology. 2019; 14: 145-146.
[80] Paez Espinosa EV, Murad JP, Ting HJ, Khasawneh FT. Mouse transient receptor potential channel 6: Role in hemostasis and thrombogenesis. Biochemical and Biophysical Research Communications. 2012; 417: 853-856.
[81] Qin X, Liu Y, Zhu M, Yang Z. The possible relationship between expressions of TRPC3/5 channels and cognitive changes in rat model of chronic unpredictable stress. Behavioural Brain Research. 2015; 290: 180-186.
[82] Kaczorowski GJ, McManus OB, Priest BT, Garcia ML. Ion Channels as Drug Targets: the next GPCRs. Journal of General Physiology. 2008; 131: 399-405.
[83] Miller M, Shi J, Zhu Y, Kustov M, Tian J, Stevens A, *et al.* Identification of ML204, a novel potent antagonist that selectively modulates native TRPC4/C5 ion channels. Journal of Biological Chemistry. 2011; 286: 33436-33446.
[84] Yu Y, Liang Q, Liu H, Luo Z, Hu H, Perlmutter JS, *et al.* Development of a carbon-11 PET radiotracer for imaging TRPC5 in the brain. Organic & Biomolecular Chemistry. 2019; 17: 5586-5594.