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REVIEW

# Transient Receptor Potential Canonical 6 (TRPC6) Channel in the Pathogenesis of Diseases: A Jack of Many Trades

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*Abstract*— The mammalian Transient Receptor Potential Canonical (TRPC) subfamily comprises seven transmembrane proteins (TRPC1–7) forming cation channels in the plasma membrane of mammalian cells. TRPC channels mediate $Ca^{2+}$ and $Na^{+}$ influx into the cells. Amongst TRPCs, TRPC6 deficiency or increased activity due to gain-of-function mutations has been associated with a multitude of diseases, such as kidney disease, pulmonary disease, and neurological disease. Indeed, the TRPC6 protein is expressed in various organs and is involved in diverse signalling pathways. The last decade saw a surge in the investigative studies concerning the physiological roles of TRPC6 and describing the development of new pharmacological tools modulating TRPC6 activity. The current review summarizes the progress achieved in those investigations.

**KEY WORDS:** TRPC6; Inflammation; Fibrosis; Signalling; Ion channels

## INTRODUCTION

Transient Receptor Potential Canonical (TRPC) channels belong to the TRP superfamily of cation channels and constitute a group of calcium-permeable cation channels [1]. Based on the structural and functional similarities, TRPC channels have been subdivided into four major subgroups, namely: TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7. The first mammalian TRPC1 channel was cloned in 1995 [2, 3]. Since then, numerous investigations have shown the involvement of these channels in various biological pathways.

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TRPC channels are expressed in many cell types and are activated by agonists of heterotrimeric G-protein-coupled receptors or by intracellular calcium store depletion. They integrate multiple signals involving the activation of phospholipase C (PLC), which catalyses the breakdown of phosphatidylinositol 4,5-bisphosphate (PIP2) to produce inositol 1,4,5-trisphosphate (InsP3) and diacylglycerol (DAG). These channels allow the influx of $Ca^{2+}$ and $Na^{+}$ ions into the cells via a pore formed by four subunits with six transmembrane domains each [4–10]. TRPC channels are regulated by multiple cellular signalling pathways, and they contribute to the pathogenesis of multiple diseases.

The current review discusses the roles of TRPC6 in the progression or development of various diseases and the signalling pathways involving in regulating TRPC6 activity. The human TRPC6 gene is located on chromosome 11 [11]; therefore, mutations in the gene may equally affect both males and females. TRPC6 proteins are widely expressed in the heart, lungs, kidneys, muscles, and the brain [12–20]. TRPC6 is a DAG-gated channel [21] which is involved in mediating a significant amount of $Ca^{2+}$ influx into the cell. Past and recent studies in human and mouse models have shown that TRPC6 dysfunction may contribute to the pathogenesis of various diseases and is associated with a facilitated disease progression. Figure 1 summarizes the roles of TRPC6 in pathological conditions ranging from increased vascular endothelial permeability, cardiac pathology, nephrological ailments, to cancer.

## KIDNEY DISEASE

### Familial Focal Segmental Glomerulosclerosis

The earliest reports about the involvement of TRPC6 in the pathogenesis of a human disease were published in 2005 [18, 22] and concerned familial focal segmental glomerulosclerosis, a kidney glomerular disease. It was demonstrated that the TRPC6 channel is localized to podocyte foot processes that are important for regulating glomerular permeability in the kidney. The authors identified several gain-of-function mutations in TRPC6, such as P112Q, S270T, N143S, R895C, and E897K, that resulted in increased TRPC6 functional activity and increased glomerular permeability leading to the development of proteinuria. Consistently, Kim and Dryer later found that TRPC6 inactivation had a protective effect against glomerulonecrosis but not age-related renal fibrosis in aged mice [23].

### Diabetic Kidney Disease

An increased expression of TRPC6 was also reported in podocytes of patients with diabetic kidney disease (DKD). TRPC6 activation has been directly linked to angiotensin II [24], which along with ROS generation is responsible for podocyte hypertrophy and associated outcomes. It was demonstrated that TRPC6 may function in conjugation with Protease-Activated Receptors (PARs) and GPCRs, contributing towards the development of glomerular injury and kidney disease in the patients presenting with diabetes. Notably, Wang et al. found that the simultaneous induction of hypertension and streptozotocin-induced moderate diabetes in the same animal leads to markedly increased albuminuria and kidney injury compared to the conditions when hypertension and diabetes were induced separately, with genetic ablation of TRPC6 significantly reducing albuminuria and kidney injury [25]. Consistently, Spires et al. also found that TRPC6 plays an important role in the development of DKD [26]. Uniquely, the authors genetically deleted TRPC6 in Dahl salt-sensitive rats (Dahl $SS^{Trpc6-/-}$ rats) and then induced type 1 diabetes in both wild-type Dahl SS rats and $SS^{Trpc6-/-}$ rats using streptozotocin. Albuminuria was not different in streptozotocin-treated Dahl SS and $SS^{Trpc6-/-}$ rats; however, the loss of TRPC6 was associated with attenuated damage to foot processes of podocytes during the development of DKD in the $SS^{Trpc6-/-}$ rats [26].

### Proteinuria and Podocytopenia

Activation of TRPC6 has been directly connected with mechanical stretch and actin reorganization in the podocytes. This in turn changes the glomerular permeability barrier, thereby adversely affecting the kidney function. TRPC6 plays a critical role in the development and advancement of proteinuria by regulating its actin cytoskeleton rearrangement in podocytes.

The pathological changes in glomerular morphology and permeability are due to the increase in TRPC6-mediated $Ca^{2+}$ influx in podocytes, and podocyte injury has been linked to diabetic kidney disease. Overactivation of TRPC6 has also been found to cause glomerular damage as this plays a role in abnormal podocyte deficiency termed “podocytopenia.” In patients with diabetes, angiotensin II levels have been found to be elevated, and it was reported that angiotensin II causes activation of TRPC6 in podocytes [27].

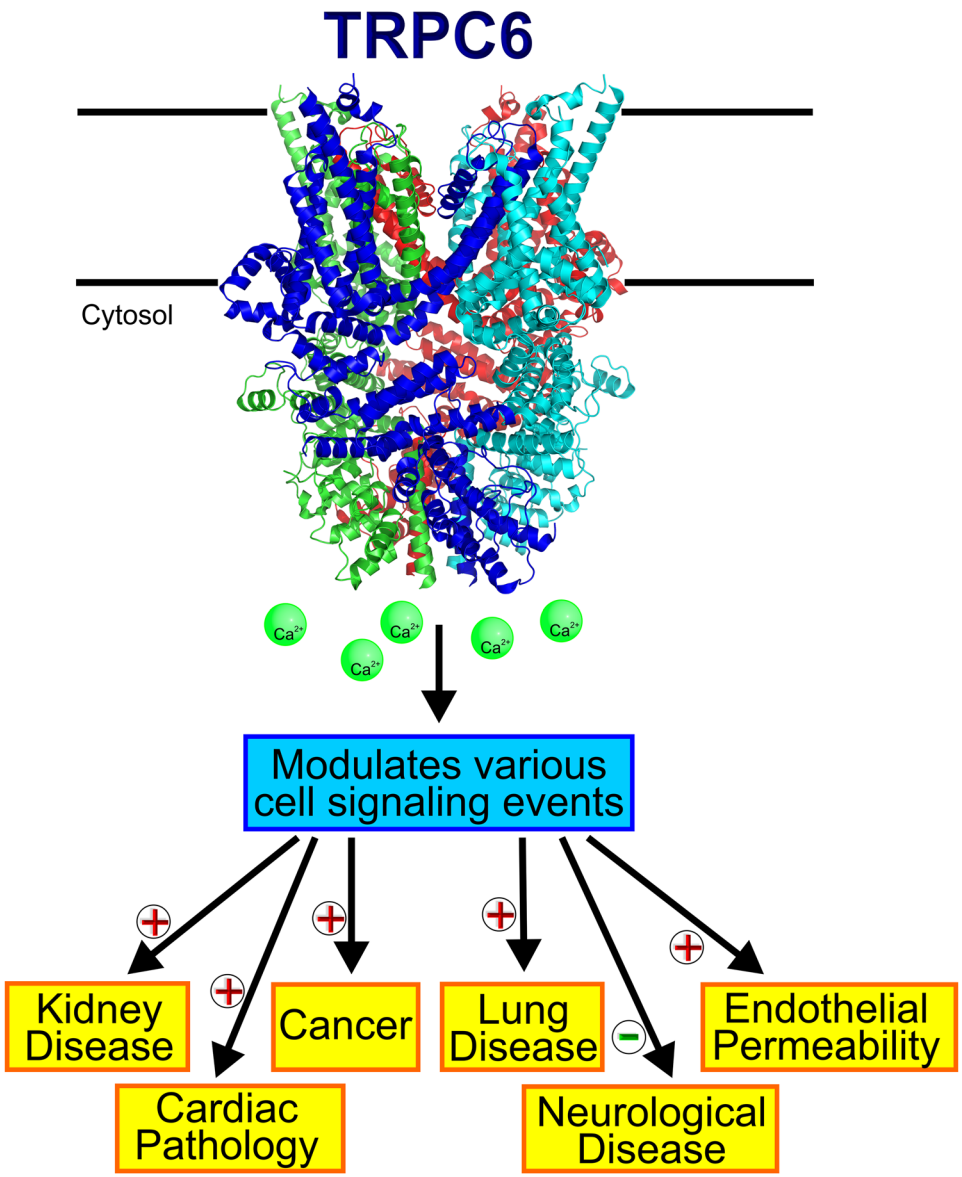


**Fig. 1** Involvement of TRPC6 signalling in various diseases and pathological conditions. The structure of TRPC6 protein was redrawn from PDB:7dxf.

## Glomerular Proteinuria

It was reported that podocyte-specific overexpression of TRPC6 led to a $Ca^{2+}$-mediated increase in RhoA activity, whilst genetic deletion of TRPC6 resulted in increased Rac1 activity and podocyte motility. The podocytes are in turn dependent on the highly organized actin skeleton for their normal structure and function. This outlines an important role for intracellular $Ca^{2+}$ in regulating the actin cytoskeleton of podocytes. The changes in podocyte number or morphology have been demonstrated to be the main cause leading to glomerular proteinuria. As the TRPC6-mediated calcium influx increases, the size selectivity of the glomerular filtration barrier by podocytes finely regulated by $Ca^{2+}$ signals gets altered due to actin cytoskeleton rearrangement [28]. These events

are the initial point of the commence of proteinuria formation. Angiotensin II is the major effector molecule which plays a pivotal role in the progression of glomerulosclerosis. It was revealed that angiotensin II increased TRPC6 expression and activated the channel leading to excessive calcium influx into the podocytes, causing the dysfunction and breakdown of the glomerular filtration barrier (GFB) with an increase in albuminuria [29]. This was further verified in other studies where angiotensin II induced NADPH oxidase 4 (NOX4) activation, thereby releasing high amount of $H_2O_2$, which in turn activates calcium influx via TRPC6 channels in podocytes. TRPC6 is a redox-sensitive channel, and its activation by Reactive Oxygen Species (ROS) overproduction may trigger injury in multiple cells including podocytes [30]. The contributions of TRPC6 channels in glomerular disease progression have been reviewed by Staruschenko et al. [31].

Some in vitro studies disclosed that high glucose levels increased TRPC6 mRNA and protein expression. Recent reports also revealed that an increased proteinuria along with reduced renal function leading to enhanced glomerular fibrosis has been directly associated with the elevated expression of TRPC6 in the model of ischaemia–reperfusion acute kidney injury [32]. Contribution of TRPC6-mediated calcium influx in podocyte injury during preeclampsia has also been proposed [33].

### Kidney Fibrosis

A study by Wu et al. [34] showed that inhibiting TRPC6 channels can help in recovery from kidney fibrosis. However, a more recent study by Kim and Dryer [35] revealed that TRPC6 inactivation can alleviate glomerulosclerosis but not renal interstitial fibrosis. A study conducted on unilateral ureteral obstruction (UUO) mouse model demonstrated that TRPC6 knockout mice had much less fibrosis compared to the wild type. In the same model, it has been shown that TRPC6 inhibition by BI-749327 ameliorates renal fibrosis [36].

In conclusion, mutations in TRPC6, as well as upregulation of its expression and activity, are directly linked to renal abnormalities such as albuminuria and podocyte cell loss that ultimately contributes to kidney damage (Fig. 2). Thus, TRPC6 is a potential therapeutic target for the treatment of kidney diseases given its widespread involvement in multiple disease-instigating pathways in the kidney of diabetic patients and experimental models.

## NEUROLOGICAL DISORDERS

TRPC6 is abundantly expressed in various regions of the Central Nervous System (CNS) [16, 37]. As a regulator of $Ca^{2+}$ influx, TRPC6 is involved in the survival of neurons, synaptic plasticity, nerve growth cone guidance, spine morphology changes, and the regulation of neurite length [38–42]. Dysregulation of TRPC6 activity may trigger a series of downstream signalling events leading to many neurobiological disorders (Fig. 3). TRPC6 along with TRPC3 play an important role in brain-derived neurotrophic factor (BDNF)-induced axon guidance and neuron survival [38]. Consistently, one study reported an increased expression of TRPC6 in hippocampus during the postnatal development [40].

### Alzheimer's Disease

Neurodegenerative diseases, such as Alzheimer's disease, are major causes of morbidity in aging population. Though the pathophysiological mechanisms may differ, $Ca^{2+}$ dyshomeostasis is common in neurodegenerative diseases [40, 43]. A significant reduction in overall expression of TRPC6 has been found in patients presenting with Alzheimer's disease and cognitive disorders [44]. Investigators discovered that TRPC6 may specifically inhibit the cleavage of amyloid precursor protein (APP) by γ-secretase and can subsequently reduce β-amyloid formation [45]. It has also been found that TRPC6 activation leads to the reduction of accumulation of beta-amyloid (Aβ) plaques in the aged brain due to increased cerebrovascular P-glycoprotein [46]. Additionally, a recent study demonstrated that repeated moderate hypoglycaemia increases the rate of Alzheimer's disease progression by decreasing TRPC6 expression and causing impairment of the TRPC6/GLUT3 pathway [47].

### Autism Spectrum Disorders

TRPC6 also plays a role in developmental psychiatric conditions such as autism. Griesi-Oliveira et al. reported [48] a decreased activity of TRPC6 in various models, including stem cell-derived neuronal cells and mouse models. They demonstrated that the reduction of TRPC6 function contributes to changes in neuronal development, morphology, and function. The authors also found that it is possible to prevent the changes in neuronal phenotypes by TRPC6 complementation in conjunction with the channel activation by insulin-like

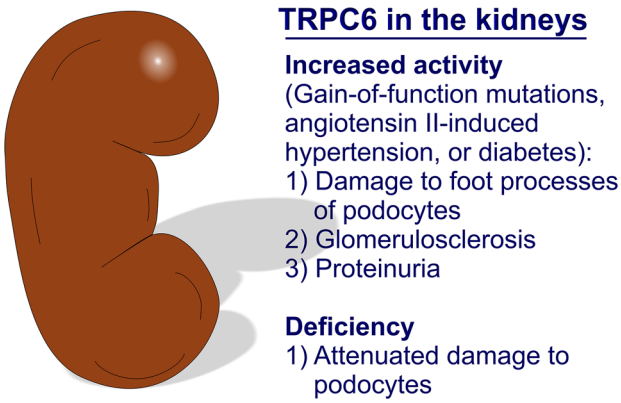


**Fig. 2** The diagram summarizes the roles of TRPC6 in the pathogenesis of kidney diseases [22–36].

growth factor-1 or hyperforin (purported TRPC6 agonists). The authors also sequenced TRPC6 in 1041 autism spectrum disorders (ASD) individuals and 2872 controls and uncovered a significant level of mutations in the ASD population, with some of those mutations being loss-of-function alterations. A more recent study by Palacios-Muñoz et al. [49] reported the consequences of TRPC6 mutations on nervous system physiology using a *Drosophila melanogaster* model. Their findings demonstrated that null mutations in TRPγ (the homologous gene of TRPC6 in the fly) led to a variety of behavioural alterations that simulated characteristics seen in ASD patients. These included deficient social interactions, impaired sleep homeostasis, defects in memory and learning, and hyperactivity. Similar to the study by Griesi-Oliveira et al. [48], this group found that treatment with hyperforin diminished the behavioural deficiencies displayed by the fruit flies.

## Cerebral Ischaemic Injury

TRPC6 overexpression has been found to protect neurons from ischaemia [50, 51]. The role of TRPC6 function was investigated using TRPC6 agonist (HYP9) and antagonist (SKF96365) in oxygen–glucose deprivation cell models and the middle cerebral artery occlusion (MCAO) mouse model of stroke [37, 52]. HYP9, which inhibited the downregulation of TRPC6 in a dose-dependent manner, led to reduced ischaemic responses, including decreased astrocytic apoptosis and cytotoxicity [52]. Conversely, SKF96365 further increased the ischaemia-associated damage. Inhibition of TRPC6 degradation by calpain inhibitors prevented ischaemic neuronal death and provided neuroprotection through the Ras/MEK/ERK/CREB pathway [37]. It has been identified in preclinical studies that TRPC6 activation may reduce neuronal death [37].

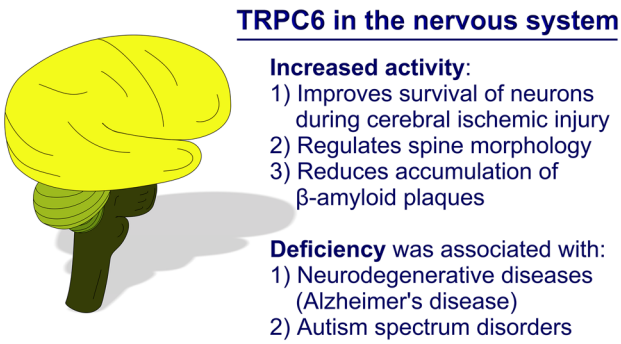


**Fig. 3** The diagram summarizes the roles of TRPC6 in the nervous system [37–52].

## CANCER

The TRPC6 channel has been highly expressed by proliferating cells, including cancer cells. Several studies have highlighted the role of TRPC6 in cancer, especially in breast cancer cells [53], which express high levels of TRPC6 [54]. Besides breast cancer, TRPC6 has also been shown to be involved in gastro-oesophageal (GE) [55], glial [56], liver [57], gastric [58, 59], renal [60], lung [61], head and neck squamous cell [62], and cervical [63] cancers.

### Breast Cancer

The role of calcium signalling in breast cancer is unquestionable. Several reports link TRPC activity with breast cancer progression [53]. Besides TRPC6 [19], TRPC1 and TRPC5 have also been implicated in the pathogenesis of breast cancer [64]. However, TRPC6 expression is the highest amongst all TRPCs in the samples of human breast ductal adenocarcinomas. Additionally, high expression of TRPC6 has been found in some breast cancer cell lines, such as MCF-7 and MDA-MB-231, that may underlie at least in part the cell lines' increased proliferation rate [65].

TRPC6 mediates multiple interactions with various proteins; some of which are directly linked to increased breast cancer progression. For example, TRPC6 associates with possible breast cancer oncogenes like large-conductance $Ca^{2+}$-activated $K^+$ (BKCa) channels, creating conditions for tumour growth [66]. TRPC6 also interacts with Fyn and Src tyrosine kinases, which may in turn activate the channel via phosphorylation events [67]. These kinases have also been reported to be overexpressed in breast cancer cell lines [68, 69]. Furthermore, the identification of TRPC6 interaction with the human myxovirus resistance protein 1 (MxA) highly expressed in triple-negative breast cancer tumours strongly suggests its role in breast cancer progression [70].

### Oesophageal Cancer

In a clinical study, high levels of TRPC6 expression were associated with poor prognosis in oesophageal squamous cell carcinoma (ESCC) patients [71]. Indeed, Shi et al. reported that TRPC6 is overexpressed in ESCC cells, and that TRPC6 is a key factor to control $G_2$ phase transition in the tumourigenesis of oesophageal cancers [55]. Thus, inhibition of TRPC6-mediated $Ca^{2+}$ influx would be beneficial to prevent ESCC progression.

### Glial Cancer

TRPC6 in association with a $Ca^{2+}$-activated channel, KCa1.1, has been considered as a potential therapeutic target for malignant glioma. Studies revealed the modulating role of TRPC6 in the increased expression and current density of KCa1.1 by interacting with the latter in vitro and in vivo [72]. The anti-proliferative effects of ionizing radiation had been found to be increased after inhibiting TRPC6 in cellular models. Also, inhibition of TRPC6 led to a reduced tumour volume in a subcutaneous mouse model of xenografted human tumours and increased mean survival in mice in an intracranial model [56].

### Liver Cancer

Hepatocellular carcinoma (HCC) cells exhibit increased SOCE possibly due to TRPC6 activity. Wen et al. [73] reported that in a xenograft model of HCC, inhibition of TRPC6 enhanced the efficacy of anti-cancer drug, doxorubicin. The authors provided evidence that the increased intracellular calcium entry via TRPC6 may be in part responsible for multidrug resistance in HCC cells.

### Renal Cancer

TRPC6 expression is markedly increased in renal cell carcinoma (RCC) specimens, and TRPC6 activity plays an important role in human renal adenocarcinoma (ACHN) cell proliferation [60]. Kim et al. reported [74] that lysine-deficient protein kinase 1 (WNK1) can activate TRPC6 via the PI4KIIIα — Gαq-coupled receptor/PLC-β in clear-cell renal cell carcinoma (ccRCC). TRPC6-mediated $Ca^{2+}$ influx in turn resulted in calcineurin-dependent activation of the nuclear factor of activated T cells cytoplasmic 1 (NFATc1) signalling in ccRCC cells, leading to their increased proliferation and migration. Importantly, inhibition of the WNK1-TRPC6-mediated $Ca^{2+}$ influx decreased NFATc1 activation and slowed down renal tumour progression. Remarkably, NFATc1 activity has been found to be elevated in tumour tissues compared to the normal tissues. These data support the hypothesis that increased TRPC6 activity may promote renal tumourigenesis.

### Lung Cancer

Several reports provided evidence that TRPC6 activity may contribute to lung cancer pathogenesis. It was demonstrated that TRPC6-mediated $Ca^{2+}$ influx in non-small-cell lung cancer (NSCLC) cells leads to increased proliferation of the cells by promoting cell cycle progression [75]. Yang et al. demonstrated that TRPC6 activity was greater in the detached cells compared to the still attached NSCLC cells and that inhibition of TRPC6 attenuated NSCLC cell proliferation and invasion. Conversely, Wang et al. reported that nicotine exposure increased TRPC6 mRNA expression and activation in non-small-cell lung cancer (NSCLC) A549 cells via a HIF-1α-dependent pathway leading to increased rate of A549 cell proliferation [76].

### Head and Neck Squamous Cell Carcinoma

Bernaldo de Quirós et al. [62] established the role of TRPC6 in head and neck squamous cell carcinomas (HNSCC). They found a significantly elevated level of TRPC6 gene transcription in HNSCC-derived cells. The siRNA-induced knockdown of TRPC6 dramatically decreased HNSCC cell invasion.

### Prostate Cancer

The Prevarskaya laboratory was the first to demonstrate that TRPC6-mediated $Ca^{2+}$ influx is important for proliferation of human prostate cancer epithelial (hPCE) cells [77] and that silencing TRPC6 by anti-sense hybrid depletion decreased proliferation of hPCE cells. The authors found that alpha1-adrinergic signalling coupled to the activation of TRPC6 and NFAT was critical for hPCE cell proliferation. Later, Yue et al. found that TRPC6 was highly expressed in human androgen-dependent and androgen-independent malignant prostate cancers, and its expression correlated with prostate cancer Gleason score and extraprostatic extension [20]. Consistently, Wang et al. demonstrated that TRPC6 upregulation is common in migrating prostate cancer cells, further supporting the role of TRPC6 in metastatic prostate cancer [78].

The pathological involvement of TRPC6 channels was also identified in the hepatocyte growth factor (HGF)-induced prostate cancer cells [79]. The study demonstrated that TRPC6 was highly expressed in DU145 and PC3 prostate cancer cell lines and its inhibition arrested DU145 and PC3 cells in the $G_2/M$ phase, thereby suppressing HGF-induced cell proliferation. Interestingly, Bernichtein et al. reported that dietary vitamin D supplementation can reduce calcium-triggered, TRPC6-mediated acceleration in the progression of prostate intraepithelial neoplasia, cell proliferation, micro-invasion, and tissue inflammation in early-stage prostate cancer [80]. Thus, vitamin D supplementation may potentially slow down prostate cancer progression by attenuating calcium-triggered tumourigenesis.

### Ovarian and Cervical Cancers

Zeng et al. reported that splice variants of TRPC6 channels with exon 3 and 4 deletions were highly expressed in ovarian cancer cells along with TRPC1, TRPC3, and TRPC4 channels [81]. Inhibitors of TRPC channels, siRNA targeting TRPC6, and blocking antibodies targeting TRPC channels decreased ovarian cancer cell proliferation, whereas overexpression of TRPC6 increased ovarian cancer cell colony growth. Therefore, the authors concluded that TRPC6 may be involved in the tumourigenesis of ovarian cancer [81]. Similarly, a high expression level of TRPC6 has been linked to increased proliferation and migration of HeLa and SiHa cervical cancer cells, further supporting the hypothesis that TRPC6 may play a pathogenic role in cervical cancers [82].

## CARDIOVASCULAR PATHOLOGY

### Hypertrophy and Heart Failure

Myocardial stretch increases cardiomyocytes' intracellular $Ca^{2+}$ levels, thereby promoting cardiac hypertrophy. It was reported that the activation of TRPC3 and TRPC6 contributes to myocardial stretch-associated slow force response (SFR) and increased $Ca^{2+}$ transient and twitch force during stretch [83]. It was also demonstrated that DAG-induced $Ca^{2+}$ signalling pathway is essential for angiotensin II-induced NFAT activation and cardiac hypertrophy during TRPC3 and TRPC6 activation. It was reported that TRPC6 can counteract hyperglycaemia-induced heart failure by disrupting the TRPC3-Nox2 complex formation [84]. Conversely, Lin et al. [36] reported that BI 749,327, a TRPC6 inhibitor, improved left heart function, reduces volume/mass ratio,

and decreased expression of profibrotic genes in sustained pressure overload mice. TRPC6 was upregulated in response to activated calcineurin and pressure overload, in failing human and mouse hearts [85]. TRPC6 responsiveness to cardiac stress in a calcineurin-dependent manner is likely attributed to two conserved NFAT consensus sites in the promoter region of the TRPC6 gene. Transgenic mice overexpressing TRPC6 in cardiac tissue had increased sensitivity to stress and heart failure [86]. It was reported that NFAT-dependent expression of beta-myosin heavy chain was increased in models of hypertrophy. TRPC6-calcineurin-NFAT signalling was implicated in pathologic cardiac remodelling resulting in fibrosis and hypertrophy in spontaneously hypertensive rats with 5/6 nephrectomy [87]. Furthermore, transgenic mice overexpressing TRPC6 in the heart developed hypertrophy and exhibited heart failure death due to cardiomyopathy [88]. Zhou et al. [89] demonstrated an increased TRPC6 expression in a 1-month post-Myocardial Infraction (MI) rat model. The administration of plant-chemical danshensu protects against ischaemia–reperfusion injury (IRI) by reducing TRPC6 expression via the c-Jun N-terminal kinase (JNK) signalling pathway. Thus, TRPC6 is a possible target for cardioprotection and its inhibition might have anti-hypertrophic effects via various cardiac signalling pathways including the ANP/BNP-GC-A [90].

### Atrial Fibrillation

Atrial fibrillation (AF) is the most common heart arrhythmia which is directly associated with mechanical stretch. Nikolova-Krstevski et al. [91] have provided evidence that TRPC6 act as an atrial mechano-sensor. The authors proposed that the stretch-sensitive TRPC6 channel may prevent atrial fibrillation under physiological conditions in the human heart by regulating paracrine crosstalk between the atrial endocardium and atrial contractile cardiomyocytes. However, chronic stretch may lead to the atrial endocardial TRPC6 internalization, precipitating atrial arrhythmia.

### Hypertrophic Cardiomyopathy

Xie et al. demonstrated that heart-specific overexpression of TRPC6 was associated with cardiac remodelling and cardiac hypertrophy [88]. The same study showed that deletion of TRPC6 in Klotho-deficient mice led to attenuation of stress-induced cardiac remodelling and cardiac hypertrophy. Overexpression of Klotho also prevented hypertrophic cardiomyopathy in these mice, improving their survival rate. The authors concluded that the Klotho's ability of reducing TRPC6 activity in cardiac muscle cells via inhibition of phosphoinositide-3-kinase (PI3K)-dependent exocytosis of TRPC6 channels may underlie the Klotho's beneficial effect in hypertrophic cardiomyopathy.

### Pulmonary Hypertension

TRPC6 is a key regulator of hypoxia-mediated pulmonary vasoconstriction and pulmonary hypertension. A unique genetic variation in the promoter region of the TRPC6 gene was linked to the facilitated progression of pulmonary vascular abnormalities in idiopathic pulmonary arterial hypertension (PAH) [92].

### Coronary Artery Disease

Upregulated TRPC6 expression was found in the smooth muscle layer of coronary arteries isolated from metabolic syndrome pigs [93], thereby showing a correlation between TRPC6 expression and increased coronary artery contractility.

Thus, the role of TRPC6 in cardiovascular pathology (Fig. 4) is beyond doubt, and hence, multiple groups all over the world are developing novel small molecules targeting TRPC6 to modulate TRPC6 activity.

## PULMONARY DISORDERS

The TRPC6 channel is expressed in human airway smooth muscle cells (HASMCs) and has an important role in the development of an array of lung diseases (Fig. 5). TRPC6 contributes to the pathogenesis of pulmonary diseases such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), asthma, lung oedema, and lung fibrosis [94–98]. The activation of Toll-like Receptor 4 (TLR4) and generation of DAG lead to TRPC6-dependent $Ca^{2+}$ influx into lung endothelial cells. This is the basic mechanism proven to be involved in endotoxin-induced lung inflammation [99].

### Chronic Obstructive Pulmonary Disease

Long-term smoking causes chronic obstructive pulmonary disease (COPD), at least in part, by increasing airway smooth muscle cell proliferation. It was reported

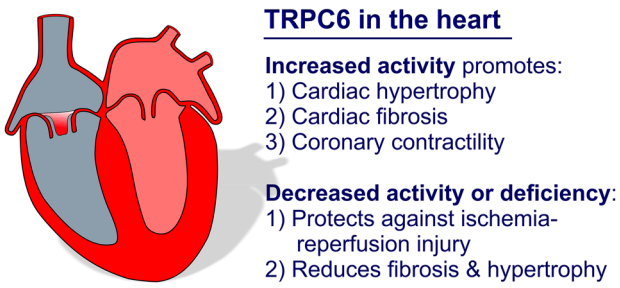


**Fig. 4** The diagram summarizes the roles of TRPC6 in the pathogenesis of cardiovascular diseases [83–93].

that nicotine can enhance airway smooth muscle cell proliferation via the α7 nAChR-PI3K/Akt-TRPC6 signalling pathway [100]. Furthermore, the pathology may also arise due to excessive alveolar macrophage activation that depends on calcium influx. Finney-Hayward et al. reported that human lung tissue macrophages expressed increased levels of TRPC6 mRNA and protein as compared with monocytes and monocyte-derived macrophages and that TRPC6 mRNA expression was significantly elevated in alveolar macrophages from patients with COPD compared to control subjects [95].

## Lung Oedema

Lung ischaemia–reperfusion-induced oedema occurs due to increased endothelial permeability that in turns results from increased activation of endothelial TRPC6. Consistently, no lung ischaemia–reperfusion-induced oedema was noted in TRPC6-deficient mice [98]. Samapati et al. reported that platelet-activating factor dependent activation of acid sphingomyelinase followed by recruitment of TRPC6 channels to caveolae increased lung endothelial permeability, with TRPC6 inhibitors preventing and direct activation of TRPC6 mimicking platelet-activating factor-induced lung oedema [101]. Furthermore, Jiang et al. reported that prostaglandin E2-PGE3 receptor 3-dependent pulmonary permeability results from TRPC6 activation in a $G_i$-PLC-SrcFK-dependent manner [102].

## Fibrosis

Published evidence indicates that TRPC6 is responsible for increased vascular permeability in the lungs which might in turn help circulating fibrocytes to migrate to the injured areas. Indeed, the TRPC6-deficient lungs exhibited a less severe pulmonary fibrosis compared to the wild-type lungs, and normal lung function was closely associated with low level of TRPC6 expression in the lungs [97].

## COVID-19

COVID-19 pathology has also been associated with TRPC6 channels. In a small clinical study including four COVID-19 patients presenting with pneumonia, TRPC6 expression was found to be markedly elevated in fibrotic lung tissue, inflammatory lesions, and cellular infiltrates [103]. Although the authors did not elucidate

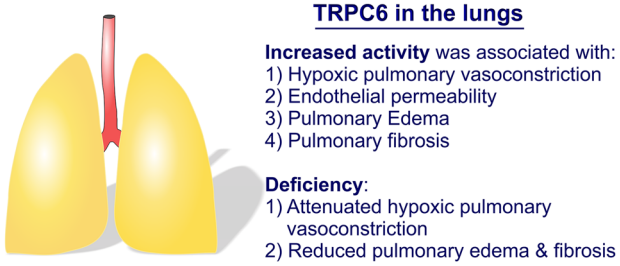


**Fig. 5** The diagram summarizes the roles of TRPC6 in the pathogenesis of pulmonary diseases [94–111].

the underlying mechanisms for TRPC6 upregulation, these findings suggest a pathological role of TRPC6 in developing COVID-19-induced complications.

### Airway Inflammation

Studies utilizing TRPC6$^{-/-}$ mice and TRPC6-selective inhibitor revealed that TRPC6 contributes to ozone ($O_3$) inhalation-induced airway inflammation. It has been shown to regulate oxidative inflammatory responses induced by $O_3$ or $H_2O_2$ through activating the ERK signalling pathway [104]. Elevated activity of platelet activating factor was also associated with increased lung vascular permeability, oedema, and inflammation. The effect was mediated via activation of acid sphingomyelinase that resulted in recruitment of TRPC6 to caveolae and the channel activation. This in turn led to increased calcium influx into endothelial cells and consequently decreased endothelial barrier function [101].

### Hypoxic Pulmonary Vasoconstriction and Pulmonary Hypertension

Increased pulmonary smooth muscle cell contractions and proliferation are long known to contribute to hypoxia-induced pulmonary vasoconstriction. In 2006, Wang et al. provided evidence that increased calcium influx observed in hypoxic pulmonary smooth muscle cells was due to an increased activity of TRPC6 channels [105]. Chronic hypoxia not only stimulated calcium influx through TRPC6 in pulmonary smooth muscle cells, but also increased the expression rate of TRPC6 via a hypoxia-inducible factor 1 transcription factor-dependent mechanism. Similar findings were simultaneously reported by Weissmann et al. who used TRPC6$^{-/-}$ mice and demonstrated that hypoxic pulmonary vasoconstriction was not observed in this TRPC6 knockout mouse model. In contrast to wild-type mice expressing TRPC6, TRPC6$^{-/-}$ mice developed regional hypoventilation-induced severe arterial hypoxemia due to the lack of hypoxic pulmonary vasoconstriction. Notably, no hypoxia-induced cation influx was observed in smooth muscle cells from precapillary pulmonary arteries of TRPC6$^{-/-}$ mice despite increased hypoxia-dependent DAG accumulation in the cells. Conversely, wild-type pulmonary smooth muscle cells exhibited significant hypoxia-activated cation currents requiring DAG accumulation [106].

Weissmann et al. did not find any correlation between TRPC6 activity/expression and chronic hypoxia-induced pulmonary hypertension [106] and later provided evidence that TRPC1, rather than TRPC6, might be responsible for inducing hypoxic pulmonary hypertension [107]. However, several other studies demonstrated that hypoxia-induced TRPC6 activation and/or upregulation may also contribute to the pathogenesis of hypoxic pulmonary hypertension [108–110]. Such disagreement may stem from the fact that cultured pulmonary artery smooth muscle cells may exhibit different properties depending on culturing conditions. Recently, Zhao et al. has demonstrated that both TRPC6 and Piezo1, which is another mechanosensitive cation channel present in lung endothelial cells, are responsible for membrane stretch-mediated influx of $Ca^{2+}$ ions in human pulmonary arterial endothelial cells (PAECs) accounting for mechanotransduction-led vascular remodelling in patients with pulmonary arterial hypertension [111].

## TRPC6 MODULATORS

The rapidly expanding role of TRPC6 in the pathogenesis of several human diseases has been fuelling the progress of TRPC6 modulator development. There have been multiple reports on various TRPC6 modulators, which include both agonists and antagonists. The usage of CryoEM approach for solving TRPC6 structures in the presence or absence of modulators allowed researchers to markedly facilitate the process of drug discovery. For example, Bai et al. have recently provided the structural insights on the TRPC6 protein interaction with its antagonist (AM-1473) and agonist (AM-0883) [112]. It appears that the antagonist makes both hydrophilic and hydrophobic interactions at multiple sites of S1–S4 and nearby helices and loops. The authors demonstrated that the positively charged piperidine moiety may form hydrogen bonds with Glu509 and Asp530 of the helices S2 and S3, respectively. The benzonitrile group may be involved in a cation-π interaction with Arg758 on the reentrant loop as well as aromatic-stacking interactions with His446 on S1 and Tyr753 on the TRP helix, whilst the indene double ring makes van der Waal interactions with Tyr612 on S4. Notably, the antagonist is 36-fold more selective for TRPC6 over its homolog TRPC3 ($IC_{50}$ ≈ 8.0 nM). Important residues on TRPC3 and TRPC6, interacting with the antagonist, are identical, except for Arg758 of TRPC6 that is replaced by a lysine in TRPC3.

The indispensability of this Arg758 for TRPC6 antagonist binding was tested by the authors [112].

## Antagonists

There have been several studies focusing on the ability of various small molecules to inhibit TRPC6 function. Such small-molecule inhibitors are critical to counteract the deleterious effect of gain-of-function mutations in the TRPC6 protein that may lead to diseases. BI 749,327 is one of the mostly used TRPC6 inhibitors. It was shown that BI 749,327 can prevent fibrosis as well as various dysfunctions in cardiac and renal diseases [113]. Notably, some derivatives of BI 749,327 are already being investigated in phase I and II clinical trials (https://clinicaltrials.gov/: NCT04665700, NCT03854552, NCT04176536). Whilst NCT04665700 and NCT03854552 are phase I clinical studies investigating BI 764,198 tolerance at different doses in healthy individuals, the NCT04176536 clinical study investigates the pharmacokinetics of a single dose of BI 764,198 in patients with moderate and severe renal impairment in comparison to a group of matched healthy individuals. Another study (NCT04604184) investigates whether BI 764,198 can improve lung health in hospitalized patients suffering from acute severe COVID-19. Another inhibitor of TRPC6, SAR7334, was used to suppress TRPC6-dependent acute hypoxic pulmonary vasoconstriction (HPV) in perfused mouse lungs [114].

A phytochemical (+)-larixol originating from European larch (*Larix decidua*) resin has been modified to derive its acetylated derivatives as selective TRPC6 inhibitors. Further, one of its methylcarbamate congeners, SH045, was shown to ameliorate lung ischaemia–reperfusion oedema in lung preparations [115]. It is a selective TRPC6 inhibitor which also attenuates renal fibrosis in an animal model of metabolic syndrome [116]. Similarly, 1-benzilpiperadine derivative (1-BP), a selective inhibitor for TRPC3 and TRPC6 channels, was effective to reduce peripheral artery disease (PAD) [117]. BTDM [(2-(benzo[d][1,3]dioxol-5-ylamino)thiazol-4-yl)((3 S,5 R)-3,5-dimethylpiperidin-1-yl)methanone] is a high-affinity antagonist for the human TRPC6 channel. Its interaction with the latter was detailed by Tang et al., 2018, who were able to determine TRPC6 structure in its presence. The authors demonstrated that BTDM binds between the S5-S6 pore domain and the voltage sensor-like domain thereby inhibiting pore opening [6]. Later, Bai et al. published two highly informative structures of TRPC6 bound with an antagonist (AM-1473) and an agonist (AM-0883), respectively. The conformational changes due to antagonist/agonist binding in the two structures allowed the authors to understand the conformational changes TRPC6 undergoes during these transition states [112]. SAR7334 designed by Maier et al. specifically inhibited TRPC6 at lower concentrations; however, at higher doses it was also inhibiting other TRPC isoforms. Its inhitory effects on acute hypoxic pulmonary vasoconstriction (HPV) and systemic BP were highly encouraging [114].

## Agonists

Because depending on the disease, both inhibition and activation of TRPC6 may be clinically useful, many research groups focused on identifying not only specific antagonists of TRPC6 but also specific agonists. For example, agonists may be useful either for treating some neurological conditions or may help in scrutinizing the role of TRPC6 activation during various in vivo experiments. Bai et al. indeed identified a relatively specific TRPC6 activator, AM-0883, that was as effective as OAG, but has a considerably higher potency. In another study, Yang et al. identified two additional agonists: M085 and GSK1702934A, which can directly activate TRPC6 via a mechanism involving residues of the pore helix (PH) and transmembrane (TM) helix S6 [118]. Recently, the pyrazolopyrimidine skeleton was identified as a TRPC6 agonist by Qu et al. using a cell-based high-throughput screening approach [119]. Additionally, the authors identified a series of potent and selective TRPC agonists. The discovery of a naturally occurring secondary plant metabolite, hyperforin, as a putative TRPC6 agonist added another aspect of targeting this channel using natural compounds [120]. Hyperforin is the main component of St. John's wort extract. It exhibits some anti-depressant properties. In addition, it was shown that hyperforin can modulate intracellular $Ca^{2+}$ levels possibly via activating TRPC6 channels. However, the ability of hyperforin to activate TRPC6 was later disputed [121].

## CONCLUSION

The role of TRPC6 channels in calcium ion permeability makes it central to various signalling pathways and thereby in disease progression. Findings from

animal and in vitro cell culture experiments have shown TRPC6 involvement in various diseases including cardiac, neurological, and nephrological diseases. The history of TRPC6 in disease pathology dates to more than 2 decades back when the first reports were published on the contribution of TRPC6 upregulation in cardiomyocyte pathophysiology in cardiac hypertrophy, cardiac fibrosis, and heart failure. Now we know that TRPC6 is involved not only in cardiac fibrosis, but also in pulmonary and kidney fibrosis. Deletion of the TRPC6 gene impacted expression of other pro-fibrotic genes in the knockout model [122]. It has been clearly demonstrated that TRPC6 can be a therapeutic target for treatment of cardiac fibrosis. Research carried out by Lin et al. (2019) found that BI 749327, a bioavailable antagonist of TRPC6, can ameliorate renal and cardiac fibrosis [36]. Role of TRPC6 has also being studied in cystic fibrosis and pulmonary fibrosis [94, 97]. Kurahara et al. (2015) has reported its role in stenotic fibrosis, a complication frequently observed in Crohn's disease [36].

Due to the critical involvement of TRPC6 in various diseases, many novel and potent antagonists have been designed, which proved to be efficacious for the cause. As this aspect is another interesting subject but beyond the scope of the current review, the readers are advised to refer to the literature for drug discovery of TRPC6 modulators.

Many recent reviews have detailed the role of TRPC6 in cardiac, pulmonary, renal, and neurological diseases. However there has been no "*one-stop shop*," where consolidated information on the role of TRPC6 in various diseases is available. Here, we provide such broad review of the literature with a bird view on many human diseases which TRPC6 may be involved in.

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## AUTHOR CONTRIBUTION

U. S., K. H., and A. G. O. designed the review. S. S., O. M., S. B., H. S., and S. M. were responsible for drafting the manuscript. U. S. and A.G.O. were responsible for the figures. M. S. B., A. G. O., and K. H. edited the manuscript.

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## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## DECLARATIONS

**Conflict of Interest** The authors declare no competing interests.

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