Review

Connexin 43: a New Therapeutic Target Against Chronic Kidney Disease?

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Key Words

Chronic kidney disease • Inflammation • Fibrosis • Connexin43 • Targets of therapy

Abstract

Chronic kidney disease is an incurable to date pathology with a continuously growing incidence that contributes to the increase of the number of deaths worldwide. With currently no efficient prognostic or therapeutic options being available, the only possibility for treatment of end-stage renal disease is renal replacement therapy through dialysis or transplantation. Understanding the molecular mechanisms participating in the progression of renal diseases and uncovering the pathways implicated will permit the identification of novel and more efficient targets of therapy. Connexin43 was recently identified as a novel player in the development of chronic kidney disease. It was found de novo expressed and/or differentially localized in various renal cell populations during progression of renal disease, indicating an abnormal connexin signaling, both in patients and animal models. Subsequent *in vivo* studies demonstrated that connexin43 is involved in mediating inflammatory and fibrotic processes contributing to renal damage. Genetic, pharmaco-genetic or peptide-based inhibition of connexin43 in animal models and cell culture systems was successful in preventing the progression of the pathology and preserving the cell phenotypes. This review will summarize the recent advances on connexin43 in the field of kidney diseases and discuss the potential of future connexin43-based therapies against chronic kidney disease.

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Introduction

Chronic kidney disease (CKD) is a major burden of public health associated with high morbidity and mortality worldwide. The number of patients suffering from CKD is constantly growing because of aging of the population, improved survival from cardiovascular diseases, and spreading of type-2 diabetes [1]. The most common causes of CKD include diabetes mellitus followed by high blood pressure and glomerulonephritis. The remaining cases can be due to polycystic kidney disease, obstructive nephropathy, pyelonephritis and others [2]. These pathologies may affect any of the kidney structures including renal vessels, glomeruli,

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and the tubulointerstitial compartment. Despite their different origin, renal diseases share common mechanisms involving inflammatory processes and the pathological accumulation of extracellular matrix which lead to gradual impairment of renal structure and function [3, 4]. Maintenance of normal renal parenchyma and homeostasis is essential for preservation of renal function and protection from CKD [3, 4]. Although our understanding of the mechanisms implicated in the development of renal diseases has been reinforced over the last years, there is a current lack of available early prognostic markers and therapeutic options against CKD, which necessitates the discovery of more targeted and efficient treatments [3, 4].

Connexins

Tissue homeostasis and structural integrity is maintained by specialized protein structures involving tight, adherens and gap junctions. Gap junctions are composed of two intercellular hemichannels, the connexons, which allow the direct communication between adjacent cells [5]. Connexons are localized on the plasma membrane of two neighboring cells and create a hydrophilic pore between the cytoplasm of the connected cells allowing the exchange of low molecular weight chemical mediators like ions (Ca^{2+}, Na^+, etc.) and second messenger molecules (cAMP, IP3, etc.) [6]. Apart from cell-to-cell communication, uncoupled connexons can exert the same functions as a complete gap junction, therefore allowing cell-to-matrix communication [7]. Connexons consist of six connexins forming a homo- or a heterohexamer. Connexins are named according to their predicted molecular weight; 20 connexin genes have been identified in mice and 21 in humans, sharing significant homology [8]. Besides specific exceptions like erythrocytes, thrombocytes mature skeletal muscle fibers and spermatozoids, gap junctions are present among all types of cells [9]. Gap junctions therefore provide a universal function as intercellular channels of communication that form the basis of direct cellular interactions. Given the relatively low specificity of gap junctions that allows passage of diverse molecules, it is not surprising that they are involved in a wide variety of physiological functions in different cell types including cell growth [10], glandular secretion [11], vascular homeostasis and angiogenesis [12], proliferation [13], bone development [14], cardiac morphogenesis [15, 16], glial function [17] and neuronal migration [18], stem cell development [19] and others.

Earlier studies have reported that several connexin isoforms are implicated in the renal physiopathology. Nearly half of the 20 members of the connexin family were found to be expressed throughout different renal compartments, at least at the mRNA level, including Cx26, Cx30.3, Cx31, Cx32, Cx37, Cx40, Cx43, Cx45, and Cx46 [20, 21]. However, connexin mRNA and protein expression do not always correlate and conflicting data regarding connexin expression and localisation have been reported. In this review we will mainly focus on the role of Cx43 in chronic renal disease.

Connexin43

Connexin43 (Cx43) is considered as the most widely expressed connexin. As is the case with other connexins, extensive studying of Cx43 has revealed that apart from its role in cell-to-cell communication, it can mediate gene transcription, cytoskeleton dynamics, ATP exocytosis, vesicle release and cell stress [22]. Cx43 is abundantly expressed in the heart and is indispensable for heart development and myocyte function [23]. Similarly, it is the most widely expressed connexin in the retina, but its role goes beyond cell communication since it can be part of a pathogenic pathway that leads to loss of retinal epithelium [24]. In contrast, vascular Cx43 has been shown to have a deleterious role in progression of atherosclerosis since reduction of its expression had a protective, possibly anti-inflammatory, effect in atherosclerosis susceptible mice [25]. In the brain, Cx43 is the main connexin in astrocytes but its exact role in neuronal physiology and neurodegeneration is disputed with contradicting

evidence on whether it exerts a neuroprotective or deleterious role [26]. In osteoblasts and osteocytes, Cx43 hemichannels are considered necessary for cell survival [27] while it is central to spermatogenesis and testis homeostasis [28]. Finally, Cx43 is expressed in several tumor types including liver, prostate, and breast. Its role in carcinogenesis and metastasis is far from straight forward since it has been shown that Cx43 can have both pro- [29] and anti-metastatic capacity in different tumors [30] which indicates a tissue or even cell-specific way of action.

Connexin43 in the kidney

Cx43 was first detected in the rat kidney in 1989 [31]. Barajas et al. provided a more complete study and concluded that Cx43 localizes in renal vasculature, mesangial cells and collecting ducts [32]. In 1997, Hillis et al. studied Cx43 expression in biopsies from patients with different inflammatory glomerulopathies and found it strongly expressed by infiltrating cells and suffering tubular epithelial cells, as well as de novo expressed in interstitial sites of injury [33]. Broadening the spectrum of renal pathologies involving Cx43 upregulation, a Japanese group reported the presence of Cx43 in normal podocytes in a linear pattern and a shift in this linear distribution in patients with diabetic nephropathy, [34] while Guo et al. reported decreased Cx43 in glomeruli of diabetic patients without specifying the cell types implicated [35]. *In vitro* data from renal epithelial cells exposed to high glucose, provided for the first time a functional explanation for Cx43 upregulation under stressful conditions, indicating that Cx43 gap junctions mediate the emission of deleterious Ca^{+2} signals [36]; however the exact role of Cx43 in the progression of renal disease remained unclear. In parallel, many studies focused on a possible role for Cx43 on renin secretion and regulation of blood pressure. Initial reports suggested that Cx43 promoted renin secretion. The replacement of Cx43 by Cx32 in transgenic mice reduced the expression and secretion of renin and prevented the renin-dependent hypertension in the 2K1C (2-kidney, 1-clip) model [37]. However, Takenaka et al. demonstrated that a specific Cx43 blocking peptide (GAP26) reduced glomerular filtration rate without altering blood pressure or renin activity, in contrast to the blockade of Cx37 and Cx40 [38]. Moreover, endothelial-specific deletion of Cx43 had no effect on renin secretion and blood pressure in contrast to mice deficient in Cx40 [39].

Connexin43 in experimental CKD

The above mentioned studies established the fact that Cx43 is expressed in the renal parenchyma and the vasculature under resting and/or pathological conditions in both animals and humans. Given its important role in cell communication and signaling it was not long before the role of Cx43 in renal pathology began to be investigated.

Renal vasculature

Renal vasculature is anatomically involved in many nephropathies resulting in CKD including hypertensive nephropathy, vascular stenosis, ischemic nephropathy, and vasculitis. Cx43 has been extensively studied in vascular pathophysiology. As reviewed elsewhere, it appears to be important for the regulation of the myogenic tone and the proliferation and migration of vascular smooth muscle cells (VSMC) [40]. In the renal vasculature Cx43 localizes, apart from VSMCs, in endothelial cells of the renal, lobar, arcuate, and interlobular arteries and afferent and efferent arterioles [41]. As mentioned above, a role for Cx43 in renin secretion and control of blood pressure has also been reported but findings are still contradicting.

To study the role of Cx43 in hypertensive CKD, we used a renin transgenic mouse model (RenTg) that overexpresses renin in the liver, causing a rapid increase of blood pressure and a

slowly progressive deterioration of renal function, thus mimicking kinetics in human disease [42, 43]. Renin overexpression gradually induced Cx43 which localized in peritubular and glomerular capillaries and correlated with the severity of the disease [44]. Alonso et al. have demonstrated than in aortic smooth muscle cells, angiotensin II induced Cx43 expression by driving NF-κB binding to Cx43 promoter [45]. To examine the potentially functional role of Cx43 upregulation, we crossed RenTg mice with Cx43 heterozygous mice (Cx43$^{+/-}$) and monitored the effect of Cx43 downregulation on the progression of the disease [46]. Partial deletion of Cx43 had no effect on blood pressure, supporting the notion that it is not implicated in blood pressure regulation. However, it significantly reduced albuminuria, inflammatory infiltrates and interstitial fibrosis. The protection from the progression of renal disease in this model was subsequently associated to a reduced interaction between endothelial and inflammatory cells. Incubation of endothelial cells with Cx43 blocking peptides reduced monocyte adhesion to the endothelial layer. Pre-incubation of monocytes with the same blocker yielded similar decreased adhesive capacity of monocytes on the endothelium. ATP release, an activator of purinergic cell membrane receptors, has been reported as a means of crosstalk between infiltrating cells and activated endothelium [47], generating pro-inflammatory signals and upregulation of monocytes adhesion molecules [48]. Cx43 has been described to mediate ATP release in several systems including neutrophils [47], microglia [49], retinal pigment epithelial cells [50], inflammatory cells [51] and proximal tubular epithelial cells [52]. Upregulation of Cx43 in renal endothelial cells could promote CKD by generating a pro-inflammatory environment that promotes leukocyte adhesion and infiltration through activation of purinergic signaling.

The podocyte

Yaoita et al. were the first to demonstrate that Cx43 is upregulated in experimental models of glomerular renal disease. Using the puromycin aminonucleoside (PAN) nephrosis model in rats, they showed that injured podocytes strongly expressed Cx43 while its expression in mesangial and glomerular endothelial cells remained unchanged [53]. Even though they provided no evidence for the role of Cx43 in podocyte pathology, they were the first to support the idea that although in basal conditions there are no gap junctions between podocytes, accumulation of Cx43 in podocytes under pathological conditions could indicate the formation of communication channels between neighboring cells. After this report, it was only nine years later when Cx43 was reintroduced in experimental nephropathy. In 2011, our group published a study on the expression of Cx43 in different models of CKD. Among other findings, we showed that in the model of nephrotoxic serum-induced glomerulonephritis (NTS-GN) in mice, Cx43 was strongly upregulated in suffering glomeruli [44]. A year later, an *in vitro* study on murine podocytes exposed to PAN pointed towards a deleterious role of Cx43 in injured podocytes [54]. Treatment of cultured podocytes with PAN induced Cx43 mRNA and protein expression and increased ROS production via NADPH activation. Gap junctions' inhibitors reduced caspace-3 activation and restored cell viability, indicating that newly formed gap junctions and/or hemichannels propagate pro-apoptotic signals in response to stress. Similar results were reported with an *in vitro* system of aldosterone-induced podocyte damage [55]. Aldosterone treatment increased Cx43 expression and gap junction formation and promoted podocyte apoptosis. SiRNA against Cx43 reversed ROS production and restored BAX/BCL-2 ratio, indicating that cell stress signals result in cell death via Cx43-mediated signaling.

Despite the increasing *in vitro* evidence for the role of Cx43 in podocyte pathophysiology, its *in vivo* importance for the progression of CKD had not yet been demonstrated. We studied Cx43 expression in biopsies from patients suffering from different types of GN including IgA and C3-GN and found a strong upregulation of Cx43 in the glomerulus [56]. To investigate whether this upregulation is related to the progression of the disease, we used the Cx43$^{+/-}$ mice in the NTS-GN model of CKD. Cx43 was strongly upregulated from early on in the progression of the disease and was de novo expressed by suffering podocytes [56]. Chromatin immunoprecipitation assays revealed that Cx43 upregulation was mediated by c-Jun and

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STAT1 binding on Cx43 promoter but not by NF-κB as previously reported in challenged arteries [45]. Cx43$^{+/-}$ mice showed more preserved renal function and glomerular structure vs. wild type mice, accompanied by less podocyte apoptosis, inflammatory infiltrates and fibrosis [56]. Mechanistically, we were able to demonstrate *in vitro* that Cx43 signaling was not restricted to promoting apoptosis. TGF-β induced phenotypic changes to cultured podocytes associated with increased expression of mesenchymal and migratory markers. Blockade of either Cx43 or purinergic signaling resulted in similar reversal of TGF-β-induced alterations, directing towards a cross-talk between ATP signaling and Cx43 deleterious actions [56]. Podocytes express a wide range of purinergic receptors including P2Y$_2$ and P2X$_7$ among others. Extracellular ATP binds to purinergic receptors activating release of Ca^{+2} from intracellular stores leading to podocyte depolarization [57]. *In vivo* imaging studies have demonstrated that propagation of Ca^{+2} waves occurs through gap junctions and mediates several pathogenic responses in the glomerulus including contraction of the glomerular tuft, increased capillary albumin permeability and acquisition of a migratory phenotype of podocytes [58].

Cx43 upregulation in stressed podocytes appears to be stimuli-independent. PAN and aldosterone mediate podocyte toxicity, while the NTS model induces inflammation and altered renal hemodynamics. In a recent study in rats suffering from obesity-related glomerulopathy, Zhao et al. demonstrated increased Cx43 expression that paralleled renal inflammation [59], while increased glomerular, probably podocyte expression of Cx43 has also been reported in a rat model of type-2 diabetes [60]. On the contrary, another study on type 2 diabetes and overt nephropathy patients has correlated the downregulation and redistribution of Cx43 expression in biopsies to the decline of renal function [61]. Conclusively, existing data indicate that the deleterious role of Cx43 in CKD may exceed its pro-inflammatory and pro-apoptotic actions. De novo expression and/or redistribution of Cx43 by suffering cells may induce responses to pathogenic stimuli and phenotypic alterations that are not yet fully understood and promote the disease in different ways.

Mesangial cells

Mesangial cells are contractile cells of the glomerulus that are in contact with other mesangial or endothelial cells via gap junctions [62]. They are considered of great importance since they maintain the glomerular structure by supporting glomerular capillaries and podocytes and regulating glomerular matrix turnover [63]. Mesangioproliferative GN, especially IgA, and diabetic nephropathy are the main types of CKD related to mesangial cells.

Using the anti-Thy 1.1 model of GN in rats, Morioka et al. demonstrated a differential regulation of Cx43 in mesangial cells vs. podocytes. While the podocyte expression of Cx43 increased in animals with GN, it decreased in mesangial cells, showing that Cx43 upregulation is not a universal response to injury in all renal cell populations [64]. In agreement with this study, exposure of cultured mesangial cells to high glucose [65] or aldosterone [66] decreased the expression of Cx43 and induced cytoskeletal rearrangements and proliferation, respectively. The effect of Cx43 on mesangial proliferation, one of the basic histological findings in IgA nephropathy, was attributed to the function of Cx43 hemichannels, since aldosterone had no effect on gap junction formation. Transient overexpression of Cx43 abolished the pro-proliferating effect of aldosterone possibly via Ca^{+2}/Protein kinase C-related signaling [66]. Treatment of mesangial cells with high glucose, a commonly used *in vitro* model to mimic diabetic nephropathy, resulted in RhoA/ROCK-mediated cytoskeletal rearrangements, translocation of NF-κB to the nucleus, F-actin accumulation and an enhanced interaction between zonula occludens-1 (ZO-1) and Cx43. Interestingly, Cx43 overexpression reversed NF-κB nuclear translocation, while ZO-1 depletion or disruption of F-actin formation prevented the reduction of Cx43 levels induced by high glucose [65]. This indicated the existence of a complex relationship between mesangial cytoskeletal proteins and NF-κB that cross-talks with Cx43 signaling. Collectively, the above studies in mesangial cells argue for a protective role of Cx43 in these cells, which could be exploited in regards of diabetic and

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IgA nephropathy where the mesangium is of primary importance. In contrast, Solini et al. have shown that changes in extracellular ATP levels, known to be controlled by the function of Cx43, regulate mesangial matrix expansion via a TGF-β-P2X7 pathway [67]. Further *in vivo* studies employing the appropriate experimental nephropathy models combined with systemic or conditional manipulation of Cx43 expression seem to be necessary to definitely uncover the functional role of Cx43 in mesangial cell-related CKD.

Tubular epithelium

Renal tubular epithelial cells are the primary or secondary target in many forms of CKD. Obstructive nephropathy and renal ischemia have a direct impact on the renal epithelium while diabetic nephropathy, hypertensive nephropathy and GN progressively impair tubules as a secondary effect. After Guo et al. reported the expression of Cx43 in tubular segments [68], a number of *in vitro* studies suggested a possible role for gap junctions/hemichannels in mediating pathological signaling in tubular epithelial cells. In renal ischemia, epithelial cells are the main cell type susceptible to damage. O_2 depletion reduces intracellular ATP levels

Table 1. Physiopathological functions of Cx43 in different in vitro and in vivo models of renal disease

Parameter	Model	Cx43 function	Reference
In vitro	Aortic smooth muscle cells treated with angiotensin II	Cx43 expression is induced through NF-κB binding on its promoter	45
	Podocytes treated with PAN	Cx43 is increased and promotes oxidative stress and apoptosis via NAPDH activation	54
	Podocytes treated with aldosterone	Cx43 expression and gap junction formation is increased promoting apoptosis	55
	Mesangial cells exposed to high glucose	Cx43 expression is decreased mediating activation of NF-κB and cytoskeletal rearrangements	65
	Mesangial cells treated with aldosterone	Cx43 expression is decreased driving proliferation via altered Ca^{2+}/PKC signaling	66
	Proximal tubular cells depleted of ATP	Cx43 expression is induced activating gap junction signaling and promoting cell death	69
	Collecting duct cells exposed to high glucose	Cx43 is upregulated which increases propagation of Ca^{2+} signals by Cx43 gap junctions	36
In vivo	Renin transgenic (RenTg) mice	Cx43 promotes adhesion of inflammatory cells to activated endothelium, Cx43+/- mice are protected against proteinuria, inflammation and interstitial fibrosis	46
	Unilateral ureteral obstruction (UUO)	Cx43 is upregulated in tubules promoting renal inflammation and decrease of E-cadherin junctions, Cx43+/- mice show preserved renal structure, Cx43 blocking peptide inhibits TGF-β-induced collagen production and MAPK activation in cultured tubular cells	44, 46
	Puromycin aminonucleoside nephrosis (PAN)	Cx43 is strongly upregulated in injured podocytes	53
	Nephrotoxic serum-induced glomerulonephritis (NTS-GN)	Cx43 mediates purinergic signaling to drive podocyte mesenchymal/migratory phenotype and apoptosis, Cx43+/- mice show preserved renal structure and function	56
	Zucker rats	Cx43 expression is increased and it is associated with renal inflammation	60
	Obesity-related glomerulopathy	Cx43 expression is upregulated in glomeruli	59
	Anti-Thy 1.1 model of mesangial nephritis	Cx43 expression is upregulated in podocytes but decreased in mesangial cells	64

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which in turn results in tubular necrosis. Taking into account that Cx43 hemichannels had been related with ATP release, Vergara et al. investigated the role of Cx43 in an *in vitro* model of ATP depletion in human proximal tubular cells [69]. ATP depletion induced Cx43 mRNA and protein expression and activated hemichannel signaling. This was also accompanied by increased cell death, but no connection between the two effects was demonstrated. Another study in tubular epithelial cells demonstrated an increase of Cx43 expression induced by TGF-β1, which triggered hemichannel function and provoked ATP release that was further linked to increased expression of interleukin 6 and fibronectin [52]. In diabetic nephropathy, secondary hypertension develops in response to chronic exposure to increased glucose concentrations. When exposed to high glucose *in vitro*, human collecting ducts responded by upregulation of Cx43 and increased Ca^{+2} signals propagation mediated by Cx43 gap junctions [36].

To study expression and localization of Cx43 in a model of tubular disease *in vivo*, we used the well-established model of unilateral ureteral obstructive nephropathy (UUO) in mice [44]. Cx43 was barely detected in control tubular cells but after UUO it was strongly expressed in tubules of both cortex and medulla. $Cx43^{+/-}$ mice showed reduced expression of leukocytes adhesion molecules and reduced macrophage infiltration. Pursuing these initial findings, we demonstrated that blocking Cx43 with antisense oligonucleotides blunted the inflammatory response in UUO and partially preserved E-cadherin junctions in tubular cells *in vivo* [46]. In subsequent *in vitro* studies, activation of tubular cells with TGF-β induced collagen production, mitogen-activated protein kinases (MAPKs) phosphorylation and expression of Sp1, a pro-fibrotic transcription factor that promotes collagen synthesis [70]. Blocking Cx43 with the GAP26 peptide blocker reduced the TGF-β effects, indicating that second messengers acting via Cx43 signaling are important for the establishment of renal fibrosis. Table 1 summarizes the current understanding of the role of Cx43 in renal diseases.

Connexin43 as a therapeutic target against CKD

Over the last years, a great effort has been made towards the discovery of novel and more efficient pharmacological targets to treat renal diseases. Cx43 has emerged as an active player in the progression of CKD, whose inhibition was proven to successfully impede the development of renal disease by arresting the progress of several inflammatory and fibrotic processes. We were among the first to show that Cx43 is upregulated and participates in the progression of renal disease in several animal models of CKD. Moreover, by using $Cx43^{+/-}$ mice we demonstrated that a reduced expression of Cx43 was sufficient to confer protection against hypertensive nephropathy, obstructive nephropathy and GN [46, 56].

Targeted therapeutic approaches to prevent Cx43 signaling involve the use of antisense oligonucleotides (AS-ODNs) and connexin mimetic peptides designed to mimic sequences on extracellular or intracellular loops of connexin proteins. The inhibition of Cx43 by AS-ODNs has been shown to dampen inflammatory responses and promote wound-healing in many tissues including central nervous system [71], skin [72-74], skeletal muscle [75], heart [76], smooth muscle [77, 78] and vascular endothelium [79-81]. Moreover, there are clinical trials using topical application of a gel containing Cx43 AS-ODNs, which have shown a safe and tolerable treatment of skin wounds, venous leg ulcers and diabetic foot ulcers [71]. In our studies, the use of AS-ODNs against Cx43 inhibited renal inflammation and fibrosis and efficiently preserved renal function in animal models of CKD [46, 56]. Notably, in all cases administration of AS-ODNs started as a therapeutic approach after establishment of the disease, which highlights the potency of Cx43 inhibition in the protection against development of renal disease.

Connexin mimetic peptides may function by either blocking the hemichannel opening or the gap junction formation, based on the protein site (intracellular or extracellular) where the peptides are designed to bind. These specific connexin blockers have been preferred the last years in cell culture and animal studies in place of classical global gap junction

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inhibitors, since their targeted action is more likely to restrict the unwanted effects on physiological functions and establish an effective regulation. The Cx43 mimetic peptides GAP19 (hemichannel blocker) and GAP26 (gap junction blocker) were proven efficient in preventing arrhythmogenesis and death in a genetic mouse model of muscular dystrophy [82], while administration of GAP26 reduced the myocardial infarct size and improved survival of isolated cardiomyocytes in a rat model of myocardial infarction [83]. In another study, Cx43 mimetic peptides significantly reduced swelling, astrocyte proliferation and neuronal loss in a rodent ex vivo model of spinal cord injury [84]. Furthermore, recent promising studies have been reported in mice suffering from myocardial ischemia where Cx43 hemichannels have been selectively inhibited with GAP19 [85]. We have recently demonstrated that blocking Cx43 with the GAP26 peptide *in vitro* prevented cell responses associated to inflammatory and fibrotic pathways, i.e. it inhibited monocyte adhesion in activated endothelium, it hampered TGF-β-induced responses in tubular cells [46] and it prevented cytoskeletal changes and apoptosis in podocytes [56]. It remains to be established whether Cx43 mimetic peptides can protect against the progression of renal disease *in vivo* in animal models.

Conclusion and perspectives

CKD reached pandemic proportions and is one of the major causes of death worldwide. Even though significant progress has been made over the last years, our understanding of the complex mechanisms driving the progression of renal disease is still incomplete. Therapeutic interventions are insufficient and especially in advanced stages the only therapeutic option is dialysis or transplantation. Cx43 was recently identified as a novel mediator of renal disease involved in central processes of inflammation and fibrosis, while its inhibition even after the initiation of the disease was capable to attenuate renal damage and preserve renal function in animal models of vascular, tubular and glomerular CKD. In this sense, novel therapies based on the targeted blockade of Cx43 in desirable cell populations may constitute a future option for efficient inhibition of the progression of CKD. Taking into account that targeted blockers of Cx43 are already available, it remains to be investigated whether they exert a protective effect in preclinical models of CKD, with a potential future application into clinical practice.

Disclosure Statement

The authors declare to have no competing interests.

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