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REVIEW

# Physiological significance of delayed rectifier $K^+$ channels (Kv1.3) expressed in T lymphocytes and their pathological significance in chronic kidney disease

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**Abstract** T lymphocytes predominantly express delayed rectifier $K^+$ channels (Kv1.3) in their plasma membranes. More than 30 years ago, patch-clamp studies revealed that the channels play crucial roles in facilitating the calcium influx necessary to trigger lymphocyte activation and proliferation. In addition to selective channel inhibitors that have been developed, we recently showed physiological evidence that drugs such as nonsteroidal anti-inflammatory drugs, antibiotics, and anti-hypertensives effectively suppress the channel currents in lymphocytes, and thus exert immunosuppressive effects. Using experimental animal models, previous studies revealed the pathological relevance between the expression of ion channels and the progression of renal diseases. As an extension, we recently demonstrated that the overexpression of lymphocyte Kv1.3 channels contributed to the progression of chronic kidney disease (CKD) by promoting cellular proliferation and interstitial fibrosis. Together with our in-vitro results, the studies indicated the therapeutic potency of Kv1.3-channel inhibitors in the treatment or the prevention of CKD.

**Keywords** Lymphocytes · Delayed rectifier $K^+$ channels (Kv1.3) · Membrane capacitance ($C_m$) · Immunomodulatory effects · Overexpression of Kv1.3 channels · Chronic kidney disease (CKD)

## Introduction

Thymus-derived lymphocytes (T lymphocytes) predominantly express delayed rectifier $K^+$ channels (Kv1.3) in their plasma membranes [1–3]. Patch-clamp studies revealed that the channels generate the $K^+$-diffusion potential across the plasma membranes, and thus play roles in regulating resting membrane potential and controlling the cell volume [4, 5]. Using selective channel inhibitors, later studies have further demonstrated that the Kv1.3 channels also play crucial roles in facilitating the calcium influx necessary to trigger lymphocyte activation and proliferation [3, 6, 7]. Concerning the molecular mechanisms that are involved, the rise in the intracellular calcium concentration activates phosphatase calcineurin, which then dephosphorylates the nuclear factor of activated T cells (NFAT), enabling it to accumulate in the nucleus and bind to the promoter of the gene encoding interleukin 2 (IL-2) [8] (Fig. 1). So far, pharmacological targeting of calcineurin has been regarded as the main mechanism by which immunosuppressive reagents, such as cyclosporine and tacrolimus (FK506), exert their effects [9]. Additionally, recent advances in functional pharmacology revealed that a selective inhibition of lymphocyte Kv1.3 channels also represses lymphocyte activity and thus suppresses cellular immunity [10] (Fig. 1). Nonsteroidal anti-inflammatory drugs (NSAIDs), macrolide antibiotics, and $Ca^{2+}$ channel blockers (CCBs) are known to exert immunomodulatory properties besides their respective anti-inflammatory, anti-microbial, and anti-hypertensive effects [11–16]. Since these drugs are lipophilic [17–20], they would directly disturb the lymphocyte plasma membranes, and thus affect the Kv1.3 channel currents when they modulate the immune response.

"Chronic inflammatory diseases" is a category of diseases for which "chronic inflammation" or "the overstimulation of cellular immunity" is responsible for pathogenesis [21]. In addition to infectious diseases and autoimmune disorders, a number of diseases such as

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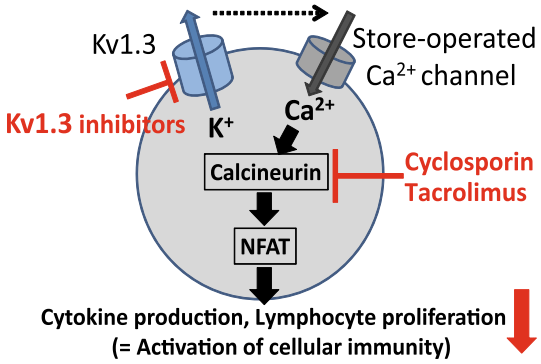


**Fig. 1** Roles of Kv1.3 channels in the activation pathway of T lymphocytes and as the targets of immunosuppressive reagents

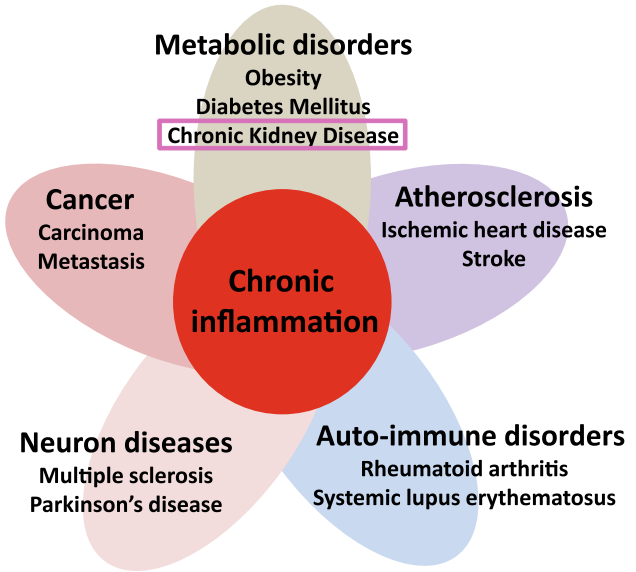


**Fig. 2** "Chronic inflammatory diseases." Chronic kidney disease also falls into this category

cancer, neuroinflammatory diseases, and metabolic disorders nowadays fall into this category [22] (Fig. 2). Chronic kidney disease (CKD) progresses relentlessly to end-stage renal disease (ESRD). The histopathology of kidneys in ESRD is characterized by tubulointerstitial fibrosis in both humans [23, 24] and experimental animal models [25–27]. Previous studies revealed the initial involvement of inflammatory leukocytes, such as T lymphocytes, macrophages and mast cells, in the development of renal fibrosis [28, 29]. Therefore, CKD is nowadays regarded as one of the "chronic inflammatory diseases" [30] (Fig. 2). Since lymphocytes are activated [31] and serum cytokine levels are greatly elevated in patients with ESRD [32, 33], the Kv1.3 channels expressed in lymphocytes would contribute to the progression of renal fibrosis in advanced CKD.

In the first part of this review article, I summarize the results of in-vitro patch-clamp studies that demonstrated that NSAIDs, macrolide antibiotics, and CCBs suppress thymocyte Kv1.3 channel currents and the membrane capacitance ($C_m$). Then, in the second part, I summarize the results of in-vivo animal studies that revealed the histopathological features of the kidneys from advanced chronic renal failure (CRF) and demonstrated the involvement of Kv1.3-channel expression in the pathogenesis. This review provides an overview of the physiological and pathological significance of the Kv1.3 channels expressed in T lymphocytes. It also provides a speculation on the key roles of the channels in the pathogenesis and treatment of CKD.

## Physiological significance of Kv1.3 channels in T lymphocytes

### Electrophysiological properties of Kv1.3 channels in T lymphocytes

T lymphocytes express a variety of ion channels in their plasma membranes, such as $K^+$ channels, $Ca^{2+}$ channels and $Cl^-$ channels [34]. The major types of these channels that have extensively been studied include voltage-dependent $K^+$ channels (Kv), $Ca^{2+}$-activated $K^+$ channels ($K_{Ca}$), $Ca^{2+}$ release-activated $Ca^{2+}$ channels (CRAC), $Mg^{2+}$-inhibited $Ca^{2+}$-permeable current (MIC) channels, and swelling-activated $Cl^-$ channels ($Cl_{swell}$) [35–39]. Among them, Cahalan et al. [1, 2] initially identified in their patch-clamp studies that human T lymphocytes most predominantly express Kv1.3-channels in their plasma membranes. In our recent patch-clamp studies, stepwise changes in the membrane potential, from the holding potential of −80 mV to the various depolarizing potential levels, evoked membrane currents in thymus-derived murine lymphocytes (thymocytes), showing voltage-dependent activation and inactivation patterns characteristic to Kv1.3 [40–43]. Additionally, since the currents were almost totally abolished by margatoxin, a selective inhibitor of Kv1.3 channels [40], they were identified as Kv1.3-channel currents.

Previous patch-clamp studies revealed that Kv1.3 channels in lymphocytes generate the $K^+$-diffusion potential across the plasma membranes, and thus play roles in regulating the resting membrane potential and controlling the cell volume [4, 5]. By generating a driving force for the calcium influx, the membrane hyperpolarization brought about by the opening of Kv1.3 channels also stimulates the calcium signaling necessary to trigger lymphocyte activation and proliferation [6, 7, 34]. Through the modification of the chemical structures of venom, scorpion, or sea anemone peptide toxins, highly selective inhibitors

of the channel have been engineered [44–47]. Recently, their immunomodulatory properties were actually demonstrated in the treatment of autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus [45, 48, 49]. In these disorders, the inhibition of the Kv1.3 channel modulated calcium influx patterns in T lymphocytes, and thus exerted immunosuppressive effects [48].

## Immunomodulatory properties of NSAIDs, macrolide antibiotics, and CCBs

NSAIDs are used in the treatment of autoimmune disorders, such as rheumatoid arthritis [50], systemic lupus erythematosus [51], and virus-triggered hypocomplementemia [52]. Studies revealed that NSAIDs inhibit the migration of leukocytes or their cytokine production either triggered by [53] or independently of [54, 55] cyclooxygenase (COX), and thus exert immunomodulatory effects. Recently, Villalonga et al. [56] have found electrophysiological relevance in this context, namely that diclofenac suppressed Kv1.3-channel currents in macrophages, and thereby impaired the migration of those cells.

Macrolide antibiotics are widely used for the treatment of a variety of bacterial infections [57]. Recently, their therapeutic efficacies as immunosuppressive agents have also been demonstrated in patients with diffuse panbronchiolitis [58], cystic fibrosis, and inflammatory bowel diseases [59]. According to several in-vitro studies, macrolide antibiotics, such as clarithromycin and azithromycin, suppress the production of pro-inflammatory cytokines from leukocytes and thus exert immunomodulatory effects [12–14]. Of all macrolides, clarithromycin most potently suppresses the production of IL-2 [12, 13], which is essential for lymphocyte activation and proliferation [56, 60].

CCBs have been demonstrated to exert immunosuppressive properties in humans [15, 16], in addition to their cardiovascular effects in hypertension and ischemic heart disease [61]. According to several in-vitro studies, CCBs, including nifedipine, verapamil, and diltiazem, repress the migration of leukocytes or inhibit their proliferation [62, 63]. Recently, using human peripheral leukocytes, Matsumori et al. [64, 65] further demonstrated that nifedipine and verapamil also suppress the production of pro-inflammatory cytokines, such as IL-1β, tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ).

## Suppressive effects of NSAIDs and macrolide antibiotics on Kv1.3-channel currents in murine thymocytes

Pprevious patch-clamp studies, including ours, have revealed the physiological mechanisms by which NSAIDs and macrolide antibiotics exert immunomodulatory properties [41, 42]. In these studies, drugs such as diclofenac sodium (0.1 mM), salicylate (0.3 mM), indomethacin (0.1 mM), and clarithromycin (30, 100 μM) were applied to murine thymocytes, and the changes in the whole-cell membrane currents were examined. Table 1 summarizes the effects of these drugs on the peak and the pulse-end currents. As previously demonstrated in macrophages [56], diclofenac sodium and salicylate markedly suppressed the Kv1.3-channel currents in thymocytes [41]. However, differing from those in macrophages, the peak outward currents were not affected in thymocytes (Table 1). Instead, these drugs significantly suppressed the pulse-end currents. Indomethacin, a more potent anti-inflammatory drug than the others, both lowered the peak and the pulse-end currents (Table 1). Clarithromycin also suppressed Kv1.3-channel currents in thymocytes [42], as previously demonstrated with voltage-dependent $K^+$-channel currents in cardiomyocytes [66, 67]. A dose of 100 μM of this drug lowered the pulse-end currents to the same extent as 30 μM (Table 1). However, it suppressed the peak currents more markedly than 30 μM, indicating the dose-dependent attenuating effects on the activation curves [66].

Since lymphocyte Kv1.3 channels trigger calcium influx, which is necessary for IL-2 synthesis [8], and since a channel blockade by highly selective inhibitors, including margatoxin and ShK-Dap$^{22}$, actually repressed the immune response in lymphocytes [56, 68], the suppressive effects of NSAIDs and clarithromycin on the channel currents were thought to contribute to their immunomodulatory properties (Fig. 3). To determine the effects of the drugs on the lymphocyte activation kinetics, more detailed in-vitro functional analyses will be required. Possible approaches in the future would include the measurement of cytokine production [60], leukocyte migration assay [56], and the measurement of [$^3$H] thymidine incorporation into the lymphocyte DNA [68].

## Effects of CCBs on Kv1.3-channel currents and whole-cell membrane capacitance

### *CCBs markedly inhibit Kv1.3-channel currents in murine thymocytes*

1,4-Dihydropyridine (DHP) CCBs, which are highly lipophilic compared to the other types of CCBs [69, 70], exert relatively stronger immunomodulatory effects [64, 65]. Among them, benidipine is one of the most lipophilic and the longest-acting [71, 72], and nifedipine is the prototype of DHPs [73]. In our patch-clamp study, nifedipine and benidipine both markedly suppressed the

**Table 1** Summary of changes in peak currents and pulse-end currents after application of NSAIDs and macrolide antibiotics

| NSAIDs | *N* | Peak current (%) | | Pulse-end current/peak current ($I/I_{peak}$) (%) | |
|---|---|---|---|---|---|
| | | Before | After | Before | After |
| 0.1 mM Diclofenac Na | 5 | 100 | 94.5 ± 4.3 | 42.0 ± 1.4 | 17.0 ± 1.9# |
| 0.3 mM Salicylate | 5 | 100 | 89.8 ± 3.2 | 52.2 ± 3.9 | 20.8 ± 2.9# |
| 0.1 mM Indomethacin | 5 | 100 | 75.9 ± 4.8# | 44.3 ± 7.4 | 29.3 ± 1.7# |
| NSAIDs | *N* | Peak current density (pA/pF) | | Pulse-end current/peak current ($I/I_{peak}$) (%) | |
| | | Before | After | Before | After |
| 30 μM Clarithromycin | 5 | 178 ± 5.6 | 111 ± 2.0# | 47.5 ± 2.2 | 15.5 ± 3.3# |
| 100 μM Clarithromycin | 5 | 277 ± 4.4 | 89.6 ± 10# | 48.5 ± 1.4 | 15.8 ± 1.0# |

Values are mean ± SEM

*NSAIDs* nonsteroidal anti-inflammatory drugs, *Diclofenac Na* diclofenac sodium

# $P < 0.05$ vs. before drug application

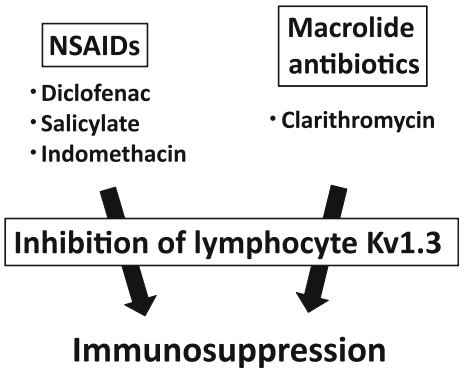


**Fig. 3** Proposed mechanism of immunosuppression by nonsteroidal anti-inflammatory drugs and macrolide antibiotics. *NSAIDs* nonsteroidal anti-inflammatory drugs

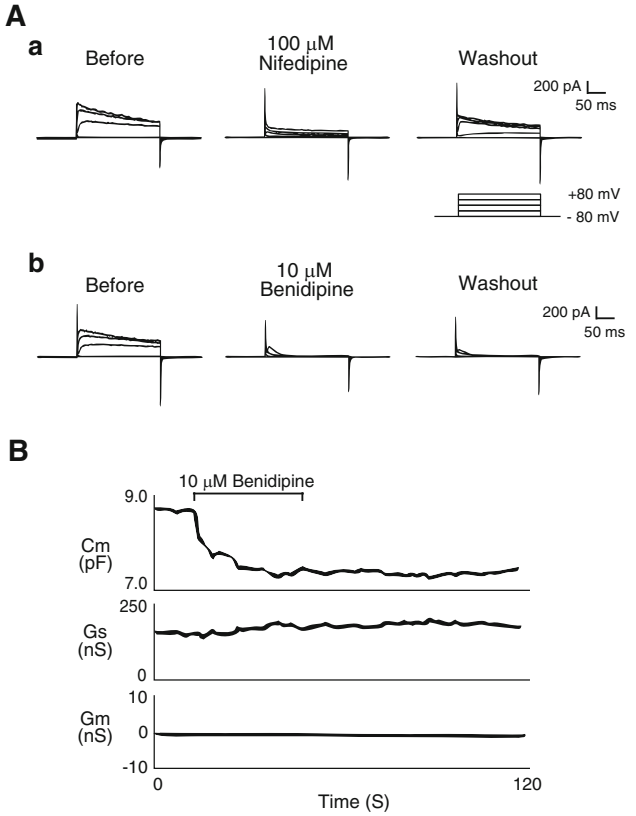


**Fig. 4** Effects of $Ca^{2+}$ channel blockers on Kv1.3-channel currents and whole-cell membrane capacitance in murine thymocytes. **A** The effects of 100 μM nifedipine (*a*) and 10 μM benidipine (*b*) on Kv1.3-channel currents. Typical whole-cell current traces at different voltage-steps recorded before and after either drug application, and after the washout. The currents were elicited by voltage-steps from the holding potential of −80 to −40, 0, 40, and 80 mV, as depicted in the voltage protocol. Each pulse was applied for a 200-ms duration between 10-s intervals. **B** Benidipine-induced changes in the thymocyte membrane capacitance, series, and membrane conductance. After establishing the whole-cell configuration, the external solution containing 10 μM benidipine was delivered for 30 s to single thymocytes. Membrane capacitance, series, and membrane conductance were monitored for at least 2 min. $N = 5$ for each trace. $C_m$ membrane capacitance, $G_s$ series conductance, $G_m$ membrane conductance. Modified from Ref. [43]

Kv1.3-channel currents in murine thymocytes at doses as low as 100 and 10 μM, respectively (Fig. 4A) [43]. Of note, benidipine almost totally inhibited the pulse-end currents irreversibly (Fig. 4Ab).

Although the effects of CCBs on cytokine production have not been directly examined [64, 65], the marked inhibition of the channel currents by these drugs strongly suggests their higher immunosuppressive potency than that of NSAIDs or macrolide antibiotics [41, 42]. Moreover, the persistent effect of benidipine on the decreased channel currents may predict its longer duration of action in thymocytes, as previously demonstrated in cardiomyocytes [72] and isolated coronary arteries [74]. Verapamil, a phenylalkylamine CCB, also suppresses Kv1.3-channel currents in various cells [75–77]. Since verapamil facilitates the inactivation of the channel currents, the drug is considered to plug into the open pores of the channel to inhibit the currents [77]. In contrast, nifedipine or benidipine induced the current inactivation on a much slower time scale than verapamil did (Fig. 4A). This represents a "C-type inactivation" pattern in kinetic studies [78], suggesting that these drugs induced conformational collapse of

the selectivity filters (inactivation gates) within pore-forming domains of the $K^+$ channels [40].

*Benidipine irreversibly decreases the whole-cell membrane capacitance in murine thymocytes*

Since DHP CCBs are known to interact with lipid bilayers of the plasma membranes [19, 20, 70], and since benidipine likely induces conformational collapse of the channels (Fig. 4A), it was conceivable that these drugs would generate structural changes in the thymocyte membranes. Microscopic changes in the cell surface area have best been monitored by the measurement of the whole-cell membrane capacitance ($C_m$) during exocytosis from secretory cells [79, 80] or thrombopoiesis from megakaryocytes [81–83]. Therefore, we employed this electrophysiological approach to detect the microscopic changes in the thymocyte membrane surface before and after the drug application [43]. Benidipine induced a significant decrease in $C_m$ immediately after the application (Fig. 4B), with minimal changes in membrane conductance ($G_m$) and series conductance ($G_s$), indicating that this drug actually induced structural changes in the thymocyte membranes. The irreversible effect of benidipine on $C_m$ suggested that the drug induced long-lasting structural changes in the thymocyte membranes.

The whole-cell $C_m$ is calculated from a parallel-plate capacitor formula: $C_m = \varepsilon A/d$, where $\varepsilon$ is the dielectric modulus of the plasma membrane, $A$ is the membrane surface area, and $d$ is the membrane thickness [84]. Assuming that $\varepsilon$ and $A$ are relatively constant before and after the drug application, the increase in $d$ is primarily considered to be responsible for the decrease in $C_m$ [85] (Fig. 5A). Since benidipine is highly lipophilic [19, 20, 70], it would disperse easily into the lipid bilayers of the plasma membrane. Therefore, the decrease in the $C_m$ (Fig. 4B) was thought to represent increased membrane thickness ($d$) as a result of the accumulation of benidipine in the plasma membrane (Fig. 5B). The accumulated drug may directly perturb the composite domains of the channels from inside the membranes (Fig. 5B). This would include the constriction or the conformational collapse of the selectivity filters within the pore-forming domains [78]. Thus, benidipine was thought to induce the "C-type inactivation" patterns of the channel currents (Fig. 4A). Benidipine, which has a higher partition coefficient than any other DHP CCBs [69, 86], would associate more strongly and dissociate more slowly with the DHP receptor binding sites in the membranes [19, 20, 70]. Therefore, benidipine was thought to accumulate in the membranes for a long period of time, causing the persistent blockade of the channel currents (Fig. 4Ab) and the long-lasting decrease in the $C_m$ (Fig. 4B).

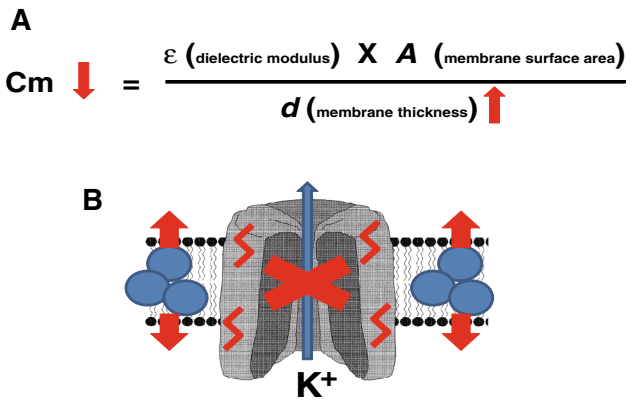


**Fig. 5** Proposed mechanism of lipophilic drug-induced Kv1.3-channel inhibition. **a** Parallel-plate capacitor formula. $C_m$ membrane capacitance. **b** Accumulation of lipophilic drugs in the plasma membrane and perturbation of the channel from inside

## Pathological significance of Kv1.3 channels in the progression of CKD

### Involvement of lymphocyte Kv1.3 channels in the pathogenesis of renal diseases

In patients with ESRD, peripheral lymphocytes are activated [31] and serum cytokine levels are known to be elevated [32, 33]. A patch-clamp study found an electrophysiological relevance in this context, demonstrating increased conductance of voltage-dependent $K^+$ channels in lymphocytes of these patients [87]. The study also revealed that the activity of the channels was deeply associated with the severity of CRF. In experimental animal models with renal diseases, such as kidney allograft rejection [88] and glomerulonephritis [89], immunosuppression by the blockade of lymphocyte Kv1.3 channels actually prevented or ameliorated the progression of the diseases. The studies demonstrated the involvement of the channels in the pathogenesis of renal diseases, for which "chronic inflammation" or "the overstimulation of cellular immunity" is responsible.

### In-situ proliferation of inflammatory leukocytes in kidneys with advanced CKD

So far, several laboratory models of CRF have been described, such as the diminution of renal mass by surgery [90, 91], ligation of renal artery branches [92], toxic nephritis [93, 94], and immunologically-induced nephritis [95, 96]. Among them, rat models with 5/6 nephrectomy (subtotal nephrectomy) followed by 8–10-week recovery periods have most popularly been studied, since they are less lethal and thus represent the stable and far advanced renal failure [97–99]. Histologically, the rat kidneys with

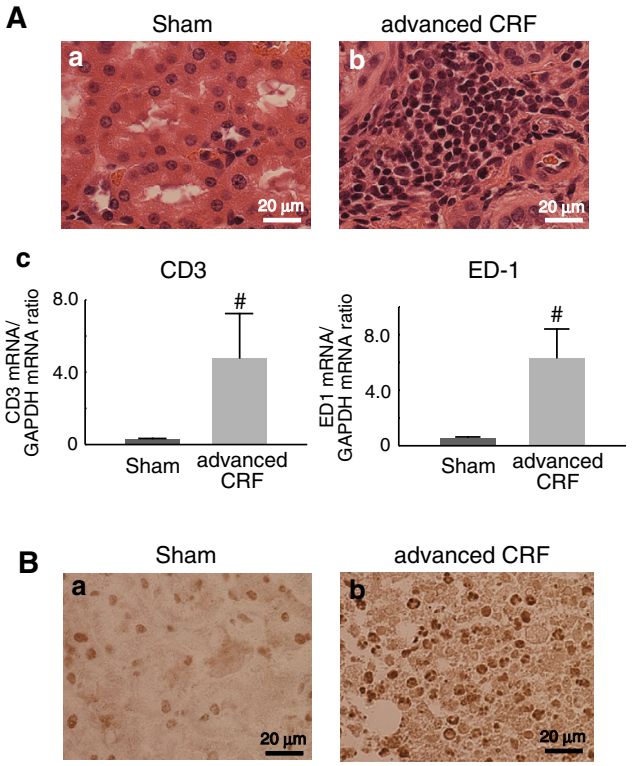


**Fig. 6** Histological features of sham-operated (sham) and advanced CRF rat kidneys. **A** H&E staining in sham-operated (sham) and advanced CRF rat kidneys. *a*, *b* High-power views of cortical interstitium. Magnification ×60. *c* The mRNA abundance of CD3 (*left*) and ED-1 (*right*) in the renal cortex of sham-operated and advanced CRF rat kidneys. $^{\#}P<0.05$ vs. sham-operated rats. Values are mean ± SEM ($N = 6$). Differences were analyzed by analysis of variance (ANOVA) followed by Dunnett's or Student's *t* test. **B** Immunohistochemistry using antibody for Ki-67 (*brown*) in sham-operated and advanced CRF rat kidneys. *a*, *b* High-power views of cortical interstitium. Magnification ×60. Modified from Ref. [100] (color figure online)

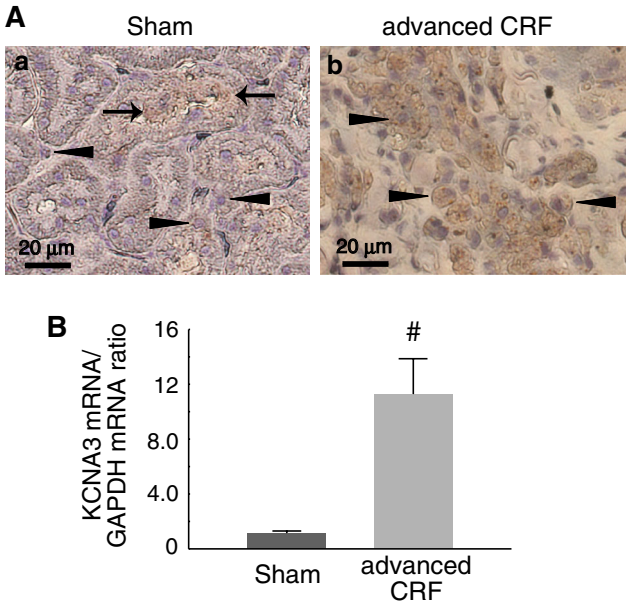


**Fig. 7** Kv1.3 expression in sham-operated (sham) and advanced CRF rat kidneys. **A** Immunohistochemistry using antibody for Kv1.3 (*brown*) in sham-operated and advanced CRF rat kidneys. *a*, *b* High-power views of cortical interstitium. Magnification ×60. Kv1.3 expression. **B** Abundant KCNA3 mRNA in the renal cortex of sham-operated (sham) and advanced CRF rat kidneys. $^{\#}P<0.05$ vs. sham-operated rats. Values are mean ± SEM ($N = 6$). Differences were analyzed by ANOVA followed by Dunnett's or Student's *t* test. Modified from Ref. [100] (color figure online)

subtotal nephrectomy are mainly characterized by severe glomerulosclerosis as a result of increased glomerular pressure and protein overload [25, 26]. In advanced stages, however, these kidneys are additionally characterized by diffuse interstitial fibrosis [27, 29], which was originally reported by Kumano et al. [28] as showing the involvement of leukocyte infiltration. In our study, rats with 5/6 nephrectomy followed by longer recovery periods were used as the model of advanced CRF [100]. In these rat kidneys, in addition to diffuse fibrosis [25, 27, 29], a large number of inflammatory leukocytes such as T lymphocytes and macrophages infiltrated into the cortical interstitium (Fig. 6Ab vs. a) with significant increases in their marker expression (Fig. 6Ac). The immunohistochemistry for Ki-67 demonstrated a number of positively stained, small round cells (Fig. 6Bb vs. a), indicating that inflammatory leukocytes were proliferating within the cortical interstitium of advanced CRF rat kidneys.

In the development of tubulointerstitial fibrosis in CRF rat kidneys, inflammatory leukocytes are initially recruited from the bone marrow and infiltrate into the renal interstitium to trigger the proliferation of fibroblasts [101]. Then, with the progression of uremia, the number of such leukocytes is considered to decrease due to the decrease in circulating lymphocyte counts [102]. In advanced CRF, however, our study demonstrated that the numbers of leukocytes in the cortical interstitium were dramatically increased by in-situ proliferation [100], showing pathological features similar to those of acute glomerulonephritis [103]. Since the cytokines produced by leukocytes stimulate the activity of fibroblasts to produce collagen [101], the increased number of leukocytes in the interstitium would promote the progression of renal fibrosis and thus contribute to the rapid deterioration of renal function in advanced CRF [100].

## Overexpression of Kv1.3 channels in the leukocytes of advanced CRF kidneys

Lymphocytes and macrophages express Kv1.3 channels in their plasma membranes [3, 56]. The membrane hyperpolarization brought about by the opening of the channels facilitates the calcium influx necessary to trigger

lymphocyte activation [6, 7, 34]. In normal rat kidneys, Kv1.3 channels are expressed in some proximal tubules [89], and predominantly in the basolateral membranes of the inner medullary collecting duct cells [104]. In these cells, the channels may contribute to the maintenance of the driving force for $Na^+$ reabsorption or play roles in cellular or total body fluid volume regulation. In advanced CRF rat kidneys, however, Kv1.3 channels were overexpressed in the proliferating leukocytes (Fig. 7Ab vs. a, arrowheads) [100], with a marked increase in its mRNA expression (Fig. 7B).

Previous studies demonstrated the overexpression of Kv1.3 channnels in cells under various pathologic conditions, including cancer [105, 106], ischemic heart disease [107], and autoimmune disorders such as rheumatoid arthritis [108] and multiple sclerosis [109]. Concerning the mechanisms involved in such overexpression of the channels, stimulation by transforming growth factor-β (TGF-β) was one of the most likely candidates demonstrated in macrophages [110]. Since uremic toxins, such as indoxyl sulfate, upregulate the expression of TGF-β [111], they might be responsible for the overexpression of the channels in leukocytes in advanced CRF. By generating a driving force for the calcium influx, the membrane hyperpolarization brought about by the opening of Kv1.3-channels stimulates the calcium signaling necessary to trigger the lymphocyte activation [6, 7, 34]. As demonstrated in cancer cells [112], the membrane hyperpolarization induced by the overexpression of the channels was thought to promote the proliferation of leukocytes. In addition to their role in cellular proliferation, Kv1.3 channels expressed in lymphocytes and macrophages trigger cytokine production from those cells [6, 7, 56]. Thus, the overexpression of the channels in leukocytes would have numerous effects on the progression of renal fibrosis.

## Therapeutic effects of selective Kv1.3-channel inhibitors on the progression of CKD

To obtain direct evidence that Kv1.3 channels expressed in lymphocytes actually contribute to the development of renal diseases, previous studies therapeutically used selective Kv1.3-channel inhibitors, such as ShK and Psora-4 [88, 89]. Margatoxin is one of the potent inhibitors of Kv1.3 channels and almost totally inhibits the channel currents in lymphocytes [40]. In experimental animal models with lung carcinoma [113], this toxin exerted antitumor activity without showing any neuromuscular side effects [114, 115]. In our study, therefore, margatoxin was used for the treatment of CKD for the first time (Fig. 8) [100]. In advanced CRF rat kidneys with margatoxin treatment, the size of the cortical interstitium was smaller, and the number of infiltrating leukocytes was much smaller

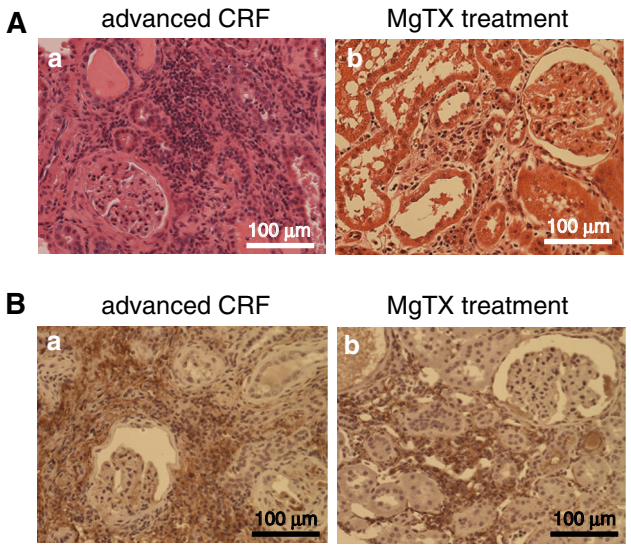


**Fig. 8** Histological features and the expression of collagen III in advanced CRF rat kidneys after margatoxin (MgTX) treatment. **A** H&E staining in advanced CRF rat kidneys with and without MgTX treatment. *a*, *b* Low-power views of cortex. Magnification ×20. **B** Immunohistochemistry using antibody for collagen III (*brown*) in advanced CRF rat kidneys with and without MgTX treatment. *a*, *b* Low-power views of cortex. Magnification ×20. Modified from Ref. [100] (color figure online)

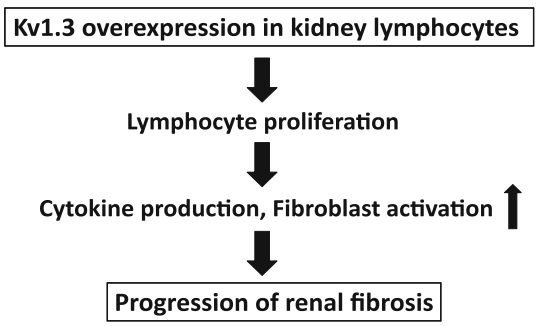


**Fig. 9** Proposed mechanism by which renal fibrosis progresses in advanced chronic kidney disease

(Fig. 8Ab vs. a). Additionally, in those kidneys, immunohistochemistry for collagen III, a marker of fibrosis, demonstrated less staining in the cortical interstitium (Fig. 8Bb vs. a), indicating that margatoxin ameliorated the progression of renal fibrosis. From these results, the overexpression of Kv1.3 channels in kidney lymphocytes was thought to promote their cellular proliferation in advanced CKD (Fig. 9). The proliferating lymphocytes were thought to be responsible for the progression of renal fibrosis, possibly through the increased cytokine production and the fibroblast activation (Fig. 9).

Grgic et al. [116] demonstrated the therapeutic efficacy of blocking the intermediate-conductance $Ca^{2+}$-activated $K^+$

channels ($Kc_a3.1$) for renal fibrosis, since fibroblasts overexpressed the channels under a pathologic condition. In a separate animal study, they also demonstrated the prophylactic efficacy of blocking lymphocyte Kv1.3 channels for kidney allograft rejection [88]. As an extension of these studies, our study further suggested that targeting the Kv1.3 channels overexpressed in leukocytes would also be useful for the treatment of renal fibrosis in advanced CRF [100]. In our series of patch-clamp studies, in addition to NSAIDs, macrolide antibiotics, and CCBs [41–43], HMG-CoA reductase inhibitors (statins) also effectively suppressed lymphocyte Kv1.3-channel currents [117]. Therefore, in this regard, besides the use of the previously developed selective blockers for the channels [44, 118], the use of these drugs could also potentially be useful as anti-fibrotic agents in patients with advanced CKD [40–43].

## Overview and future directions

T lymphocytes predominantly express Kv1.3 channels in their plasma membranes. Patch-clamp studies showed physiological evidence that some commonly used drugs, such as NSAIDs, macrolide antibiotics, and CCBs, suppress the channel currents in lymphocytes, and thus exert immunosuppressive effects.

According to animal studies using rat models with advanced CRF, the overexpression of lymphocyte Kv1.3 channels contributed to the progression of renal fibrosis by promoting cellular proliferation. Since the channel inhibition actually ameliorated the progression of the disease, this channel could be a potent therapeutic target for advanced CKD and possibly for other "chronic inflammatory diseases". Several in-vitro studies, including ours, strongly suggested the therapeutic usefulness of potent Kv1.3-channel inhibitors, such as NSAIDs, macrolide antibiotics, and CCBs, in the treatment or the prevention of CKD.

Besides lymphocytes, Kv1.3 channels are also expressed in other types of hematopoietic cells, such as megakaryocytes [81, 82, 119], and in various types of cancer cells [105, 106]. Therefore, our future tasks would include revealing the as of yet unknown significance of the channels in a variety of physiological or pathological conditions, such as thrombopoiesis and tumor progression.

**Conflict of interest** The author declares that he has no conflict of interest.

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