Translational Nephrology

Potassium channels: the ‘master switch’ of renal fibrosis?

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Summary of key findings of the article

Progressive renal fibrosis resulting from proliferation of interstitial fibroblasts is hallmark of chronic kidney failure, whatever the origin. The intermediate/small-conductance Ca\(^{2+}\)-activated K\(^+\) channel (KCa3.1) promotes mitogenesis in several cell types by altering the membrane potential, thus enabling extracellular Ca\(^{2+}\) entry. Grgic et al. evaluated the role of KCa3.1 in renal fibroblast proliferation, testing whether deficiency or pharmacological blockade of KCa3.1 suppressed development of renal fibrosis. Mitogens stimulated KCa3.1 in murine renal fibroblasts via a MEK-dependent mechanism, while selective blockade of KCa3.1 inhibited fibroblast proliferation by promoting G0/G1 arrest. In a classical model of renal fibrosis, mouse unilateral ureteral obstruction (UUO), robust up-regulation of KCa3.1 was detectable in affected kidneys. KCa3.1 KO mice showed reduced expression of fibrotic marker expression, less chronic tubulointerstitial damage, collagen deposition and α-smooth muscle cells after UUO, with better preservation of functional renal parenchyma. The selective KCa3.1 blocker TRAM-34 similarly attenuated progression of UUO-induced renal fibrosis in wild-type mice and rats. Thus, Grgic et al. believe that KCa3.1 is involved in renal fibroblast proliferation and fibrogenesis, suggesting that KCa3.1 may serve as a therapeutic target for the prevention of fibrotic kidney disease.

Keywords: chronic kidney disease; fibroblasts; intracellular calcium; KCa3.1 channels; renal fibrosis

Review of the field

Two decades of research into the nature of progressive kidney disease have highlighted the role of fibrosis—that is, glomerular and tubulointerstitial scarring—as a common endpoint of almost all forms of renal damage [1,2]. While much is known about the molecular background of fibrosis and the growth factors and cytokines that prompt fibroblasts or transdifferentiated kidney cells to release collagen and matrix components [3,4], the search for a single ‘master switch’ that initiates the process remains elusive. This would be extremely important, as targeting this key factor or signal would enable us to ‘turn off’ fibrosis and perhaps the progressive loss of renal function that plagues millions of individuals worldwide [5].

The paper by Grgic establishes a link between fibrosis and transmembrane ion fluxes, namely K\(^+\) and Ca\(^{2+}\) via the intermediate/small-conductance Ca\(^{2+}\)-activated K\(^+\) channel (KCa3.1; KCNN4; SK4) (Tables 1 and 2). These channels regulate K\(^+\) efflux (apoptotic volume decrease), and by activation of caspases, directly inhibited by cytosolic K\(^+\). KCa3.1 have sensitivity of these channels, usually activated by [Ca\(^{2+}\)], slightly below 1 µM. It has long been known that KCa3.1-mediated Ca\(^{2+}\) influx is associated with vascular inflammation, atherogenesis and proliferation of endothelial cells, T lymphocytes, macrophages, vascular smooth muscle cells, fibroblasts etc. [7–11]. Cell proliferation is believed to follow K\(^+\) efflux and Ca\(^{2+}\) entry as a result of Ca\(^{2+}\)-dependent growth factor gene expression, along with activation of cyclins and kinases involved in cell division. K\(^+\) channel activity seems required for the G1–S transition. On the other hand, proliferation is limited by enhanced apoptosis, resulting from cell shrinkage upon K\(^+\) efflux (apoptotic volume decrease), and by activation of caspases, directly inhibited by cytosolic K\(^+\). KCa3.1 have also been implicated in transcellular chloride secretion and cyst growth in autosomal-dominant polycystic kidney disease [12]. The investigators herein provide multiple lines of evidence that KCa3.1 critically control renal scarring. First, mitogens upregulate the channel (which has weak baseline activity) in murine renal fibroblasts. Second, TRAM-34...
blocks bFGF-stimulated proliferation of these cells. Third, mouse unilateral ureteral obstruction (UUO), a classical model of renal fibrosis [13], is associated with increased KCa3.1 gene expression. Fourth, KCa3.1 KO mice fail to develop fibrosis in response to UUO. Finally, TRAM-34 similarly blocks fibrosis in UUO mice. This is a neat experimental approach, as often seen in previous years for growth factors and cytokines implicated in kidney fibrosis such as transforming growth factor-β1 [14], bone morphogenic protein-1 [15], platelet-derived growth factor [16] and hepatocyte growth factor-1 [17], among others.

However, the ‘fibrosis master switch’ model has its drawbacks. First is its uniqueness. A review by Boor et al. identified in 2007 some 17 target mechanisms of kidney fibrosis, successfully counteracted by no less than 80 different experimental approaches, including blocking Abs, inhibitors and receptor antagonists [5]. The likelihood of a ‘one-fits-all’ mechanism is low, based on current understanding of the complexity of tissue healing through fibroblast activation [18]. Second, blocking fibrosis may not be enough to rescue a kidney from progressive failure. ‘True repair’ would also involve regeneration of specialized cells and reshaping structures that have been lost. Terminal differentiation of the adult kidney seems to be the major obstacle to regenerative medicine [19].

Third, even though fibrosis may well be triggered by overwork of surviving intact nephrons, most data point to a key role of the initial renal injury, which progressively extends over time to the residual nephrons. Damage to the filtration barrier in diabetic glomerulopathy or experimental glomerulonephritis, for example, is an ongoing process, further amplified by tubular overload and interstitial inflammation [20].

Fourth, under most circumstances, fibrosis follows when inflammation subsides. As sustained inflammation accompanies most forms of renal injury [20], cutting off the deposition of collagen would leave untouched the primary process that yields nephron loss over months to years in the human kidney. Interestingly, no differences in mononuclear cell infiltration were noted in KCa3.1−/− mice, in comparison with their UUO wild-type littermates.

Finally, murine models of fibrosis suffer from the strong tendency of this species to heal lesions through scarring. The kidney of higher mammalians has a much longer lifespan and a definitely slower rate of collagen fiber deposition. Inhibition of KCa3.1 would have to last for years to ward off fibrosis in chronic diseases such as pyelonephritis or diabetic nephropathy, with unknown effects on excitable tissue and extrarenal organs expressing this channel.

**What is it for the practicing nephrologist**

The time has not yet come for the practicing nephrologist to directly interfere with the fibrosclerotic evolution of renal disorders [5]. To date, the one and only effective approach to slow down decay of renal function is still renin–angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors, ANG II receptor antagonists or perhaps renin inhibitors [5]. Yet, work like this one by Grgie et al. may shed light on some mechanisms of fibrosis that can be soon pharmacologically targeted to delay progression of renal failure. Interestingly, such an approach would possibly bypass the serious adverse effects of RAS inhibitors, including fragile renal haemodynamics, acute worsening of renal function, hyperkalaemia etc. What is still unclear is whether there is a common pathway leading to fibrosis.
independent of the nature of renal injury, or rather that each individual disease leads to scarring of the kidney via different mechanisms [5]. Moreover, we need to know how relevant proteinuria is to tubulointerstitial damage, for example, and whether diabetic nephropathy or a glomerulonephritis with the nephrotic syndrome are equally sensitive to KCa3.1 blockade as this non-proteinuric model of UUO. Finally, it is necessary to assess whether, similar to UUO in mice, KCa3.1 plays a role in human kidney fibrosis, whether they could be safely inhibited for a certain length of time and then to eventually design a controlled randomized clinical trial with repeated biopsies. We have a long way to go, indeed. In the meantime, our patients will likely have to rely on their renoprotective regimens for a while.

**Take-home message**

Renal fibrosis can be targeted in experimental animals by manipulation of intermediate/small-conductance KCa3.1 channels: a potential step forward in the quest to prevent progressive renal disease.

**Acknowledgements.** Supported by funds from Italy’s Ministry of University and Scientific Research (MIUR) to P.M. (Ricerche di Facoltà).

**Conflict of interest statement.** None declared.

**References**


Received for publication: 27.10.09; Accepted in revised form: 28.10.09