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Review article

The critical role of tubulointerstitium in renal disease progression

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Background: Recent works have demonstrated that, regardless of the primary causes, tubulointerstitial (TI) fibrosis is the major cause of progression of renal failure.
Objective: To summarize the mechanisms of progression and regression of TI damage.
Results: Experimental studies have shown that there are three common processes of progressive TI damage: injury, inflammation, and fibrosis. Renin angiotensin system (RAS) blocking agents could substantially decrease these lesions.
Conclusion: The fulcrum of the balance between progression and regression of TI fibrosis remains to be elucidated but would be related to the activation of RAS.

Keywords: Progression, regression, renal failure, tubulointerstitial fibrosis.

The final histology of renal disease, regardless of the primary kidney process, usually consists of glomerulosclerosis and tubulointerstitial fibrosis comprising tubular atrophy, missing of peritubular capillary network, and accumulation of matrix in the interstitial area [1]. As the history of nephrology began with a passion for glomerular structure, pioneer researchers had focused on glomerulosclerosis as a cause of progressive renal disease. Other authors suggested that tubulointerstitial lesions were related more to renal function than glomerular damage. In 1844, Henle et al studied kidney sections of a girl who died from renal disease and noticed that tubulointerstitial damage seemed to be more impressive than glomerular injury [2]. Unfortunately, this observation had been forgotten.

Further understanding of the mechanisms of renal progression came from an established remnant kidney model. In 1932, Chanutin and Ferris recognized that rats, that had significant kidney mass removed, gradually developed glomerulosclerosis and renal failure [3]. Obviously, these findings resemble the human condition although the underlying mechanisms were still not understood. In 1985, not so long after the establishment of micropuncture and the emergence of the Wistar rats, a landmark study by Hostteter and Brenner was published [4]. These investigators demonstrated early onset of glomerular hemodynamic adaptation after renal mass reduction. The change was mainly due to a higher degree of decrease in afferent rather than efferent arteriolar tone, leading to increases in single nephron glomerular capillary flow, intraglomerular pressure and, finally, single nephron glomerular filtration rate (SNGFR). This phenomenon is considered as a short term adaptation but leads to glomerulosclerosis. The main reason for the increased SNGFR is increased glomerular capillary pressure through relatively poor dilatation of the efferent arteriole compared with the afferent arteriole. This hyperfiltration theory provided new insights to the mechanism of progression and became a core for many current treatments [5]. However, accumulating data during the past decade reintroduced what Henle et al described a hundred years ago, that renal function is closely related to interstitial not glomerular damage.

Tubulointerstitial damage and fibrosis are now widely accepted as a cause of progression of renal failure. A rapid understanding of the molecular mechanisms of tubulointerstitial damage has accumulated and can be divided into three processes, injury, inflammation, and fibrotic phases [6]. Current

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knowledge regarding inflammation and fibrosis do not identify renal specific mechanisms for these two processes as being parts of tissue healing. Identifying injury factors is crucially important. Proteinuria, hypoxia, and oxidative stress are considered as major injuries, all of which are related to renin angiotensin system (RAS) activation. These seem not enough to explain all of the processes. Indeed, work during the past several years shows evidence of partial resolution of renal lesions mostly glomeruli, when animals were treated with extremely high doses of RAS blocking agents [7]. These results open a new chapter in nephrology.

The progression

Tubular cell injury

Many pieces of indirect evidence indicate that there are multiple episodes of tubular injuries during the course of progressive renal disease [8]. If the insults are too severe, there will be tubular cell loss via apoptosis or necrosis. Tubular cells respond to sublethal injuries by producing many cytokines and growth factors which enhance inflammation, fibrosis, and even tubular cell proliferation. The chronic episodic insults interfere with normal healing and turn the kidney into a scar. Identifying the key insult(s) is of importance in moving the fulcrum toward regression.

After a significant nephron loss, the remaining nephrons increase their work to compensate by enhancing SNGFR, glomerular hypertension, and hyperfiltration. The adaptive process also takes place in renal tubules. Tubular hypertrophy might be a result of the trophic effect of vasoactive molecules especially angiotensin II (ANG II) [9]. The workload of each remnant tubule is enhanced in parallel with the heightened SNGFR. Structural hypertrophy of a tubular cell is accompanied by an augmented workload. Apical and basolateral transporters increase in number and function [10]. The amount of ammonia generation, as a part of acid regulation per each tubular cell, increases [11]. In order to maintain adequate energy, hypertrophic tubular cells enhance their oxygen consumption and number of mitochondria [10]. The increased oxygen demand makes these cells more susceptible to hypoxic injuries. Whether this tubular adaptation leads to permanent structural damage is still an unsolved question. However, recent work by Nath and colleagues suggests that the increased ammonia production might elicit a deteriorating effect by activating complement and inflammation which could subsequently injure the tubular cells. Alkali treatment attenuated tubular injury by decreasing ammonia generation [12].

Oliver in 1939, by performing serial sections and carefully examining each glomerular structure, noticed that a significant proportion of glomeruli did not connect with tubules [13]. The finding of atubular glomeruli was confirmed by later studies. The likely pathogenesis is that the severely damaged tubule did not survive and lost contact with the glomerulus. Such a glomerulus progressed to glomerulosclerosis. On the other hand, some hypertrophic tubules, after tracing back, did not attach to the glomeruli and were called aglomerular nephrons. These tubules then atrophied.

Tubular cells that are exposed to ultrafiltration fluid act as a final regulator of body homeostasis by means of reabsorption and secretion. In general, ultrafiltration consists of electrolyte and waste with very small amounts of leaked macromolecules [14]. Under physiologic conditions, tubular cells tend to reabsorb rather than secrete these leaked macromolecules. Injured glomeruli pass a large amount of the leaked macromolecules. Many of these molecules carry toxicity to tubular cells. Proteinuria is the most extensively investigated molecule [15-17]. Proteinuria is found in almost all forms of progressive renal diseases in human and animal models. Glomerular hyperfiltration is believed to be a major cause of proteinuria in the remnant renal model, whereas glomerular basement membrane dysfunction may play a role in the glomerulopathy model. At first, several nephrologists paid attention to proteinuria as a marker of renal damage. In 1954, Oliver et al found accumulation of protein droplets in tubular cells, indicating that protein might not be just a simple marker [15]. Remuzzi and Bertani suggested that proteinuria itself might be toxic to the tubular cell [14]. The model for studying renal toxicity from preoteinuria is puromycin-induced nephropathy. In this model, animals are given aminoglycoside and puromycin. Within a week, massive proteinuria developed accompanied by tubulointerstitial inflammation. Supporting data came from human diseases, such as diabetic nephropathy. Indeed, the amount of proteinuria is related to the progression rate. Therefore, proteinuria is currently considered as a prognostic marker of progression in various glomerular diseases. However, the mechanisms of how proteinuria injures the tubular cell

are not yet fully understood. *In vivo* work demonstrated evidence of proximal tubular cell injury after exposure to proteinuria. Nuclear factor-κB (NFκB) and activator protein-1 (AP-1) are important transcriptional factors which are activated by proteinuria and albumin [16]. These two molecules are pivotal activators of inflammatory cytokines including interleukin-1 (IL-1), tumor *in vivo* necrotic factor (TNF), monocyte chemoattractant protein (MCP-1), regulated upon activation, normal T-cell expressed and secreted (RANTES), and osteopontin. All of these could induce further inflammatory responses at the adjacent interstitial area [17]. NFκB, on the contrary, has anti-apoptotic property. Thus, the tubular cell itself might gain from NFκB activation. A complement pathway is also activated by proteinuria *in vivo* and *in vitro* (see later). One of the most quoted mechanisms is endocytosis protein which could damage lyzosome. Again, this hypothesis is still not proven.

The type of proteinuria might be an important factor. Although albumin is a major fraction of proteinuria, the toxic role of albumin remains inconclusive. A recent study induced massive proteinuria with minimal glomerular structure change. It was done by injecting a slit diaphragm with the antibody mAB 1-5-6 [18]. This model is very similar to minimal change disease in humans. Although the authors could observe tubular cell injuries, they were mild when compared with other models, and these lesions might be related to the amount of proteinuria. To date, it is still uncertain whether puromycin is totally free of tubular toxicity. Indeed, puromycin-induced nephrosis in analbuminemic rats had the same degree of tubular damage [19]. Data in human diseases are also inconsistent. Minimal change disease and the majority of membranous nephropathy with nephrotic range protienuria are considered very slow progressive diseases. Moreover, patients with hypertensive nephropathy, polycystic kidney, and Alport's syndrome develop end-stage renal disease (ESRD) independent of the magnitude of proteinuria or albuminuria. These noteworthy data cause many nephrologists to hesitate about concluding that progressive renal diseases are mediated mainly by albuminuria.

On the other hand, albumin bound with fatty acid [20], iron or transferin [21], and other proteins is more toxic than the unbound albumin. Transferin may be capable of inducing complement membrane attack complex, C5b-9, formation on the tubular membrane. In humans, interstitial damage and progression are usually described in glomerular disease with non-selective proteinuria. This suggests that the bound albumin, which is non-selective proteinuria, might be a major toxic substance for the tubulointerstitium. Lipiduria is now considered a renal toxic condition as well. Recently, albumin bound fatty acid was found to be more toxic to tubular cells than free albumin [22]. One possible mechanism is likely mediated by the activation of the peroxisome proliferators-activated receptor (PPAR) pathway. A recent human study found that kidney function loss was more rapid for those patients who had lower HDL [23]. However, renal disease is not a feature of dyslipidemia. Eddy examined the effect of lipid overload by feeding single kidney rats with a high cholesterol diet [24]. After 12 weeks, interstitium damage occurred, supporting the involvement of lipid in kidney damage. Treatment of dyslipidemia in renal impaired patients with HMG Co-A reductase inhibitor may be promising in decreasing progression.

Since tubular injuries develop after glomerular injuries, one possibility is that the damage to tubular cells might be caused by leakage of inflammatory mediators through the urinary space. The amount of urinary cytokines correlate with disease activity. When glomerular disease is in remission, spilled over cytokines are reduced. IL-6 and complement are found in the urine of glomerulonephritis patients [25]. Considering their sizes, complements might pass from glomeruli with nonselective proteinuria. The amount of urine C5b-9 in membranous nephropathy indicates more severe disease. Because micropucture had been performed in only a few studies, one cannot conclude that these urinary cytokines are glomerular in origin but are actually from very early tubular cell sources. It is hypothesized that glomerular mediators might leak into post-glomerular peritubular capillaries and cause the upregulation of adhesion molecules in this area. However, it is very difficult to prove this hypothesis.

The kidney is predisposed to injury by the complement system. The brush border of the proximal tubule can activate the alternative pathway. A complementary protein family, decay accelerating factor (DAF), CD 59 in humans, and Crry in rodents are constitutionally expressed in this area [26]. Proteinuria alters the renal complement regulating system and activates the complement cascade which

leads to sublethal injury of the tubules [27]. C5b-9 complex, an activated product of the common pathway, is deposited in the tubular cell. Urinary complement in various kinds of renal disease is strongly correlated with the degree of proteinuria. In the remnant kidney model, Abbate et al demonstrated C3 deposit at the site of high protein reabsorption. This area was infiltrated with inflammatory cells. Therefore, proteinuria, complement, and inflammatory cells combine in tubular injuries. Matsuo's group studied the role of complement in single kidney rats injected with mAB 1-5-6 [28]. These authors showed that tubular injuries were related to proteinuria and complement activation along the tubule. Complement depletion by snake venom decreased tubular but not glomerular damage [29]. Tubular damage in the puromycin model was less in C6 deficient rats. In the remnant model, there were no significant changes in complement repleted animals in the early phase. However, long term follow up clearly showed that C6 depleted rats had better renal function and histology even where proteinuria did not differ [30]. The other important finding was that C6 deficient animals showed improvement in histology at day 70 compared with day 35. This message strengthens the role of complement in progression and confirms that renal tissue has the capacity for repairing itself. Indeed, the kidney is able to produce complement as well. Tubular cells can generate C3 as well as C4 in a pathologic condition but the function of renal origin complement is not clearly understood [31]. The adaptive responses after tubular cell loss, combined with systemic acidosis, increase production of ammonia which can initiate complement activation and further damage tubules by modifying C3 to activate amidated C3 [32].

In general, SNGFR is increased after significant nephron loss (**Fig. 1**). Actually, the response to nephron mass loss in each remaining nephron is quite heterogeneous especially in the later phase. SNGFR varies from one third to three times of normal. Glomerular blood flow in each remaining nephron also varies in a wide range. This heterogenicity might generate some poorly perfused nephrons and tubules. Activation of RAS is one of the most important underlying mechanisms of glomerular hyperfiltration. In addition, after nephron loss, many vasoconstrictive molecules are increased while there are decreased natural vascular relaxants. Therefore, each diseased kidney is put into a heterogeneous vasoconstrictive state which is prone to develop intrarenal shunting, leading to hypoperfusion areas. Fine et al postulated that hypoperfusion might generate a hypoxic environment which promotes renal fibrosis. Recent work demonstrated the presence of hypoxia in an early phase of the diseased kidney in remnant, glomerulonephritis, and puromycin nephropathy models [33, 34]. Some pieces of evidence also suggested that activation of intrarenal angiotensin may contribute to a major part of intrarenal hypoxia [33].

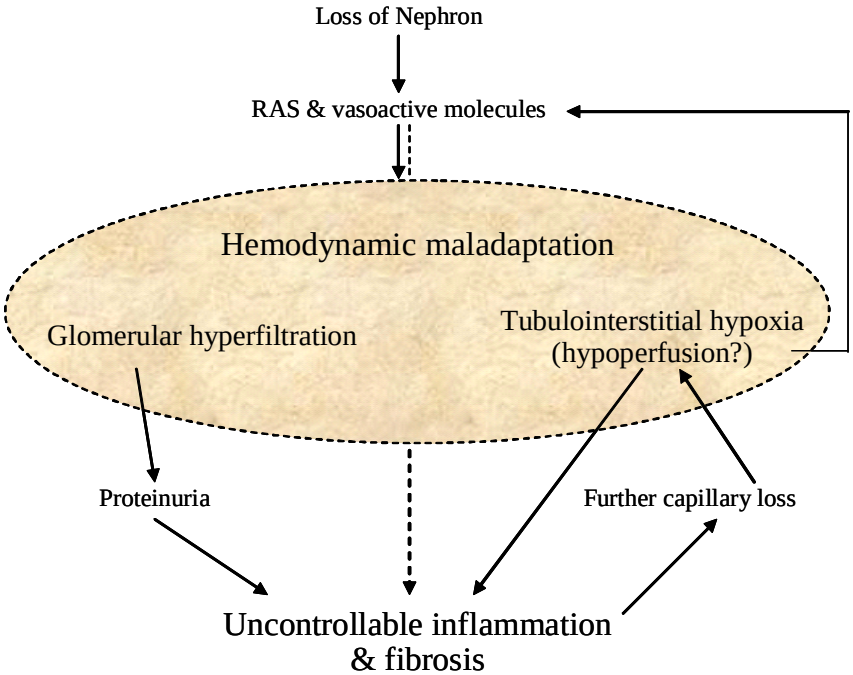

Fig. 1 Hemodynamic maladaptation. RAS = renin angiotensin system.

Hypoxia is also found in many fibrotic conditions including hypertrophic scar, pancreas, and liver fibrosis [35]. Proximal tubular cells produce inflammatory and fibrotic cytokines when cultured in hypoxic condition as well as with TNF, intercellular adhesion molecule-1 (ICAM-1) [36], and osteopontin [37]. All of these are important in macrophage trafficking. Collagen I and IV synthesis was also increased. Moreover, renal fibroblasts were activated by hypoxia [38]. A recent study showed that the tubular cell changes its phenotype to be a myofibroblast in chronic hypoxia [39]. Loss of the post-glomerular peritubular capillary network that could potentiate hypoxia was reported in remnant and unilateral ureteral obstruction (UUO) models after fibrosis was well-developed [40]. Extensive studies of human biopsies by Bohle's group provided the evidence that the peritubular vascular area is significantly lost during the course of renal disease progression and there is a strong negative correlation between the vascular damage and renal function [41]. However, the lack of reliable methods to measure or, at least, to demonstrate hypoxic cells *in vivo* leaves this hypothesis waiting to be verified.

Tubulointerstitial inflammation

Infiltration of inflammatory cells is always found during the course of renal disease progression. The role of inflammation in renal progression is generally recognized. Almost all known inflammatory mediators have been tested in every study model of progressive renal diseases. These strong and reproduced data strengthen the role of the inflammatory process in renal disease progression. The exact role of this process is not yet fully known. Most studies demonstrated a favorable short term outcome when the inflammatory process is reduced, but the long term outcome is still unknown. Many workers demonstrated poorer outcomes on histological evaluation during the later phase. Since the inflammatory process is a defense mechanism, what is detected might be the healing and clearing of devitalized tissue. Current data also do not support the role of autoimmunity, including uncontrolled inflammation, to justify immunosuppressive therapy which has serious side effects. But some anti-inflammation drugs seem promising [42].

The injured tubules produce abundant numbers of inflammatory cytokines and chemokines. NFκB is an important transcriptional factor that is upregulated in the renal tubule. This molecule regulates a broad range of cytokines including IL1 as well as IL 6. *In vitro* studies showed that the NF pathway was activated after the tubular cell was engulfed by protein [43]. Target transcription of truncated IκB, which inhibits active NFκB, could limit renal injury in the protein overload model. TNF and IL-1 also participate in the progression of renal disease. Both are the common earliest cytokines that can be found in any injured cell. A recent study of the UUO model found that the tubular cell increased production of TNF after four hours of UUO [44]. Local effects of TNF and IL-1 include initiation of the inflammatory process by producing downstream mediators, enhancing vascular adhesion molecules that are important for mononuclear cell trafficking, and activating lymphocyte. IL-1 could also induce the tubular cell to produce fibronectin and could transform the tubular cell to be a myofibroblast-like cell via transforming growth factor-β1 (TGF-β1) dependent pathway [45]. TNF receptor knock-out animals had less interstitial fibrosis in the UUO model [46]. Short term treatment with anti IL-1 receptor antagonist in the glomerulonephritis model decreased macrophage infiltration but had little effect on fibrosis [47, 48]. IL-6 is one of the earliest cytokines that is upregulated in the injured tubular cells. IL-6 is not only involved in lymphocyte activation but also contains anti-inflammatory actions [49]. Tubular cells, in the model of tubolointerstitial nephritis and diabetic nephropathy, produced IL-6 [50]. This molecule had strong influence on T cell activation. Mice engineered to overproduction of IL-6 had focal glomerulosclerosis and tubulointerstitial damage. These animals, like many genetically engineered models, suffered from several illnesses. It seemed imprudent to conclude that the renal injuries were the result of IL-6. The vascular adhesion molecule, including the vascular cell adhesion molecule-1 (VCAM-1), ICAM-1, and selectin, were also up-regulated during this phase even in tubular cells. This finding should be considered as a part of the inflammatory process [51].

A group of chemoattractant molecules also plays an important role in the recruitment of inflammatory cells. The main sources are tubular cells and infiltrating inflammatory cells. Chemokine (C-C motif) ligand 2 (CCL2) and MCP-1 are important for monocyte trafficking [52]. Almost all forms of tubular injuries mentioned above were associated with up-regulation of MCP1. Genetically engineered animals with target disruption of MCP-1 had decreased

amounts of interstitial macrophage influx [53]. Osteopontin, an acidic glycosylated phosphoprotein, was essential for macrophage influx in the early phase. In addition, complement activation also participated in interstitial inflammation.

Apart from the classical mediators, ANG II has been involved in the inflammatory process as well. Administration of exogenous ANG II to animals initiated intra-renal inflammatory cascades [54]. This may be due to the pro-inflammatory effect of ANG II mediating via ANG II receptor type2 (AT2 receptor). It should be noted that this finding is kidney preferential since the inflammation in other organs develops somewhat later than that occurring in the kidney. AT2 receptor is up-regulated in the remodeling tissue. *In vitro* administration of ANG II to cultured tubular cells elicited hypertrophy rather than initiation of an inflammatory process, suggesting that ANG II may not directly initiate the inflammation. Indeed, a recent study reported that NFκB was activated in Cos7 cells transfected with AT2 not AT1 receptor in the presence of ANG II [55].

Infiltration by inflammatory cells is always found in the histological examination of all chronic renal diseases. The recruitment of these inflammatory cells occurs in the early phase of the disease. Macrophages infiltrated as early as three hours after ureteric ligation [56]. Since inflammatory cell appearance is closely correlated with tubular injury, it was postulated that the injured tubular cells might activate and get involved in macrophage and lymphocyte trafficking by means of cytokine and chemokine. The role of the macrophage in renal progression has been extensively investigated [57]. The activation and trafficking of macrophages is mediated via both T cell dependent and independent pathways. Macrophages induce tubular cell apoptosis, disruption of normal tubulointerstial matrix, and reactive oxygen species (ROS) that are potent cytotoxic substances [58]. Decrease of macrophage infiltration by radiation, drugs, or selectin disruption seems to show favorable short-term results [59]. However, the long term outcome is inconclusive. Diamond and colleague reported a good long-term result from macrophage depletion by essential fatty acid restriction in puromycin-induced nephropathy [60]. It should be noted that the AT2 receptor is essential in macrophage recruitment as well. A recent report on chimeric animals, transplanted with AT1 receptor knockout bone marrow, showed more severe renal fibrosis as well as renal progression although macrophage infiltration was significantly reduced. This finding suggests that macrophages had a pivotal role in regulating matrix balance. There are many types of macrophages involved in the inflammatory process. Some types are mainly targeted to destroy pathogens, non-viable cells, and even normal cells. Other types could promote the healing process, lay down a new matrix, and support cell regeneration [61]. It seems likely that the latter group of macrophages work under the effect of profibrotic cytokines especially the TGF superfamily [62]. Each macrophage might turn its function toward these two ends. These new insights have therapeutic implications since, to date, we cannot discriminate which is which. Our non-selective treatment might ruin the good effect as well as limit the bad ones. Immuno-modulation therapy shifting macrophages to the good role is an interesting strategy. The time point of intervening might be important as well. Using a novel transgenic mouse which expressed human diphtheria toxin under a c11b promoter, Duffied et al. specifically ablated the machrophage within a minute [63]. With this animal, the authors showed limited liver regeneration after depleting macrophages but in experimental glomerulonephritis this ablating of the macrophage showed a protective outcome. The mechanisms of how lymphocytes are present in this lesion are not yet understood. To date, many investigators believe that these lymphocytes are attracted by a nonspecific antigen pathway especially the chemokine system [64]. Previous work attempting to verify specific antigens was inconclusive. In a cadmium-induced renal injury model, heat shock protein 70 (HSP 70) was identified as a target antigen to activate T cells [65]. A similar role of HSP 70 in progressive renal disease remains unexplored and the role of antigens involved in progressive renal disease is still obscure. It should be noted that in pathological condition(s), the tubular cell can act as the antigen-presenting cell which might activate both T and B cells. A recent study demonstrated the selective upregulation of interferon-inducible protein-10 (IP-10) at a peritubular capillary in a rat model of thrombotic microangiopathy [66]. Blocking the IP-10 pathway by means of a neutralizing antibody significantly decreased T lymphocyte infiltration in tubulointerstitial areas. Recently, there was a study suggesting that this chemokine might be involved in lupus nephritis [67]. Some studies found that mycophenolate mofetil as well as tacrolimus attenuated

renal progression in the remnant kidney model by decreasing macrophage infiltration. Both drugs act mainly on the lymphocyte activation pathway, suggesting the important role of T cell dependent macrophage function in progressive renal disease [68].

Tubulointerstitial fibrosis

Tubulointerstitial fibrosis occurs after inflammation. Much literature labels tubulointerstitial fibrosis as the final common pathway of progressive renal disease as a static lesion. In fact, tubulointerstitial fibrosis is a dynamic process; the involution and resolution of fibrosis might occur at all times. The characterization of fibrosis is the expansion of extracellular matrix and destruction of normal tissue architecture. Collagen I, III, IV, and VI, and fibronectin are the major matrices that have been observed. Under physiologic conditions, the amount of extracellular matrix (ECM) is finely regulated by a balance between production and degradation. This normal balance is destroyed in fibrotic renal disease. Myofibroblasts as well as fibroblasts are matrix producing cell, and are markedly increased while matrix degradation is unorganized and significantly decreased. Most of these changes are believed to be a consequence of damaging tubule and inflammatory process.

In general, fibrosis takes place after inflammation. Most profibrotic cytokines contain anti-inflammation properties. Some of the vasoactive substances and inflammatory cytokines can directly induce fibrosis or transcriptional factor of profibrotic cytokines [69]. The most important profibrotic cytokines which involve renal fibrosis are TGF β1, platelet derived growth factor (PDGF), connective tissue growth factor (CTGF), and fibroblast growth factor (FGF) [70]. Of these, TGF β1 shows the strongest evidence. This molecule is ubiquitously found in all cases of progressive renal disease [69, 71]. TGF β1 mRNA and level correlated well with fibrotic activity. Any method that can decrease the TGF β1 level gives favorable results [71]. Tubular cells and infiltrating mononuclear cells are the main sources of TGF β1 production. Angiotensin as well as albumin can induce tubular cells to produce TGF β1 [72]. The action of TGF β1 consists of activating fibroblasts, turning tubular cell into myofibroblasts, inducing fibroblasts, myofibroblasts, and tubular cells to produce ECM, and inhibiting matrix degradation enzymes by inducing transcription of tissue inhibitor of metalloproteinase (TIMP). Most of this action is mediated by the Smad and MAPKK pathway [71, 73]. As previously mentioned, TGF β1 is also crucial in regulating macrophage function in healing. It should be recognized that TGF β1 is a crucial growth factor in wound healing but the overall action of TGF β1 in the progression of renal disease seems inappropriately high. PDGF is a potent vasoconstrictor and is increased in progressive renal disease. PDGF induces fibroblast proliferation [69] while CTGF acts downstream to TGF β1 in fibrogenesis.

To date, there are few identified natural antifibrotic growth factors that might slow renal fibrosis. Interferon gamma (IFN-γ) is an apoptotic factor for fibroblasts and myofibroblasts. Direct infusion of IFN-γ to the kidney diminished fibrosis in the remnant model [74]. Hepatocyte growth factor (HGF) seems to contain general features of the healing process without promoting fibrosis. The action of HGF consists of decreasing TGF β1 and PDGF as well as opposing the action of TGF β1. Treatment of the remnant model and puromycin-induced nephrosis with HGF reduced interstitial fibrosis [75]. Bone morphogenetic protein 7 (BMP-7), a member of the TGF superfamily, has anti-fibrotic activity [76]. Vascular endothelial growth factor (VEGF) has been reported to retard renal progression. This growth factor acts by promoting angiogenesis, as a paracrine, in order to maintain cell-vascular contact. Cellular hypoxia is the strongest factor in inducing VEGF production by parenchymal cells although VEGF receptor locates at the adjacent endothelium.

In the kidney, podocytes and collecting tubules constitutionally express VEGF [77]. The injured tubular cells in the remnant and UUO models decreased VEGF expression which is correlated with the loss of peritubular capillaries. Exogenous VEGF administration could restore the vascular network, decrease fibrosis, and slow renal disease progression. In disagreement with these studies, VEGF seems to promote fibrosis in the diabetic model.

Myofibroblasts, which express mesenchymal markers and alpha smooth muscle actin, are markedly increased in the fibrotic area. In the normal kidney, myofibroblasts are present in small numbers. This cell is believed to be a major matrix-producing source. The number of interstitial myofibroblasts is well correlated with interstitial damage and renal function [78, 79]. Not only in the kidney, myofibroblasts

are found in every healing wound. The presence of myofibroblasts is essential for the repair and arrangement of new matrix. TGF-β1 is an important survival factor for myofibroblasts. After the repairing process is complete, TGF-β1 decreases and myofibroblasts are believed to be cleared by apoptosis. The origin of renal myofibroblasts is also interesting. Accumulating data show that these mesenchymal cells can be transformed from epithelial cells [78, 79]. In progressive renal disease, under the persistence of a high level of TGF-β1, most of the myofibroblasts were derived from renal tubular cells. Ng and co-workers showed the gradual phenotypic change of tubular cells into myofibroblasts in the remnant model [80]. CTGF, IL-1, advanced glycation end product (AGE), and hypoxia also induces in vitro tubular EMT as well [81]. Blocking the Smad pathway, HGF, and BMP-7 inhibits *in vitro* EMT [82]. In the *in vivo* study, EMT was found in all progressive renal models and human renal tissue. Besides myofibroblasts, tubular cells are capable of transforming into fibroblast. Okada et al. treated tubular cells with a combination of profibrotic cytokines and found that many of these cells express fibroblast specific protein (FSP) [83]. Myofibroblasts, activated fibroblasts, tubular cells, and leucocytes participate in matrix production. Unlike many tubular responses which are also noted in injured cells, the expression of mesenchymal marker and change of cell phenotype are not generally identified. Cell phenotype is tightly regulated by epigenetic mechanisms. The inhibition of this regulation is fascinating and might be a key factor for regeneration.

Interstitial matrix degradation is controlled by a group of proteinase enzymes. Matrix metalloproteinase (MMP), a zinc dependent endopeptidase, is the main regulator of matrix balance in the kidney [84]. The action of MMP is governed by its inhibitor protein family, TIMP. The amount of TIMP is increased in progressive renal disease. This is partly under the influence of TGF-β1. Hypoxia induces TIMP activation as well. On the contrary, a TIMP-1 knock-out animal did not show reduced tubulointerstitial fibrosis in the model of UUO or overload proteinuria, suggesting that TIMP-1 might not be the important mechanism in renal progression [85]. In the MMP group, MMP2 and MMP9 seem to have a bigger role in renal fibrogenesis. Previous work indicates that increased MMP activity lessens the degree of tubulointerstitital fibrosis. Indeed, the story is more complex since MMP could also degrade tubular basement membranes. Adhesion to tubular basement membranes is an important external factor for tubular cells in maintaining their phenotype. Plasmin is another key enzyme that regulates renal matrix balance. Plasminogen activation inhibitor 1 (PAI-1) inhibits plasminogen conversion to plasmin. PAI-1 is not usually expressed in the normal kidney but increases in many pathological conditions including overload proteinuria, radiation nephropathy, UUO, and remnant model86. PAI-1 in knock-out mice decreased interstitial fibrosis in the UUO model. Surprisingly, macrophage infiltration was also reduced. Angiotensin II and TGF-β1 increase the transcription of PAI-1 and, therefore, decrease plasmin expression. Plasmin itself could activate TGF-β1 by cleaving TGF β1 from the binding protein. Thus, the interactions among TGF β1, PAI-1 and plasmin might modulate one another.

The regression

As mentioned above, one should recognize that renal scarring is a part of the healing process. As such, it might be possible that after the primary insults are eliminated, a regenerative process will take place [87]. Severe short term insults in ischemic tubular necrosis almost completely recover. This is also true in the case of severe glomerular damage in rodents of the Thy1.1 model, suggesting that renal regeneration power may persist in the case of short term structural damage. However, renal regeneration power in chronic damage is virtually abolished. Thus, understanding the normal regeneration process as well as its regulation is of importance for future therapeutic intervention.

Renal regeneration

It is known that the mammalian metanephrons has a very limited ability to regenerate. The human kidney is completely developed before birth while the rodent's kidney fully develops within the first few weeks of life. After that, no new nephron is generated. In contrast, some animals retain the nephrogenesis power throughout life. A recent study of elasmorbrach fish reported an area of nephroblastema that generated new nephrons in adult fish [88]. When a major part of the kidney was removed, the skate fish rebuilt its kidney unlike the mammal. Studies in salamander limb regeneration suggest that regeneration needs to start from time zero when the whole organ begins to develop. The mammalian kidney begins with a ureteric

bud approach to the mesechymal cell. The interaction with the ureteric bud induces the mesenchymal cell to differentiate into an epithelial cell, or in other words with "Mesenchymal Epithelial Transdifferentiation (MET)". By far, MET is likely to be an important process in development since it reverses to EMT in the fibrosis schema. One optimistic hypothesis proposes that tubular EMT may finally turn into MET and heal the kidney. In this scenario, a myofibroblast might turn into tubular cell. However, to date, there is no evidence suggesting the presence of MET in the fully developed kidney. Indeed, myofibroblast undergoes apoptosis rather than transdifferentiation.

A study of short term and recovery injury reveals that tubular cells express several embryonic genes which are usually found in the development of the kidney and these include PAX-2, Lim1-2, engrailed, noggin, and Notch [89]. This reflects the recapitulation process at least at the cellular level. The loss of ability to express these embryonic genes may hamper healing power in renal progression but this area remains to be investigated.

Stem cells and renal progenitor cells

Several studies show that extrarenal stem cells may contribute to renal regeneration [90]. Renal engraftment of transplanted stem cells appears in tubules, mesangium, and even podocytes. However, the number of these engraftments was considered too low and varied, depending on the detection techniques. A recent study confirmed that the major source of renal repairing cells were neighboring cells rather than of extrarenal origin [91]. Studies to identify renal-specific progenitor cells are in progress [92]. Several groups report potential cells that might be progenitor cells. Despite differences in isolation techniques, cellular property and localization, most of the potential cells reside in the renal medulla which has relatively low oxygen tension. This would be the essential property of a stem cell niche. Loss of renal progenitor cells may alter the repairing power during renal progression. However, the role of renal progenitor cells in repairing the kidney remains uncertain even in reversible injuries.

Determinant of renal repair

In the beginning, tissue damage in the reversible model of Thy 1.1 and in ischemic reperfusion injury is more severe than that of the remnant kidney model. Paradoxically, only the latter progresses toward unhealed scar. This disparity suggests that the renal regeneration power may be preserved in the case of short term structural injury but is totally reduced in chronic damage. The most important question is what is the determinant of renal regenerative power? It should be noted that regenerative power is not equal in different tissues. In the kidney, mesangial cells proliferate during active disease and undergo apoptosis soon after the underlying disease subsides. This is also true for the glomerular endothelium. However, the situation in podocytes may differ. The podocyte is a terminally differentiated cell, in which intracellular cyclin-dependent inhibitor is sustained at a high level. This cell is a major source of glomerular VEGF which is essential in maintaining glomerular structure. Loss of podocytes, which is believed to occur via the loss of VEGF, will lead to glomerulosclerosis. The podocyte that enters the cell cycle loses its phenotype [93]. Proliferation of podocytes is observed in a group of diseases for example HIVAN which is characterized by a malignant form of glomerulosclerosis [94]. Therefore, podocytes might be the critical determinant of glomerular recovery. Heretofore, no such podocyte-like cells were identified in the tubulointerstitium. Indeed, the tubular cell has very high regenerative power and should not be critical in determining renal fate. Peritubular capillary networks seem to have lower regenerative power than tubular cells. However, the peritubular capillary and interstitium capillary are almost completely recovered in ischemic acute tubular necrosis (ATN). A more possible structure in determining regeneration may be the tubular basement membrane (TBM). As previously mentioned, loss of TBM per se initiates EMT and an inflammatory cascade. Tubular regeneration in ATN occurs on a TBM frame. A complete loss of TBM, noted in extremely severe ATN, is associated with poor regeneration.

Evidence of regression

Being an optimist, one must look for the evidence of regression. Several groups of investigators showed partial recovery of glomerular lesions and some degree of tubulointerstitial lesion improvement through super high doses of ACEI and ARB [95, 96]. In addition, Koo et al demonstrated enhancement of recovery of tubulointerstitial lesions by ACEI treatment in a model of reversible UUO [97]. These findings strengthen the old and very familial concepts that renal

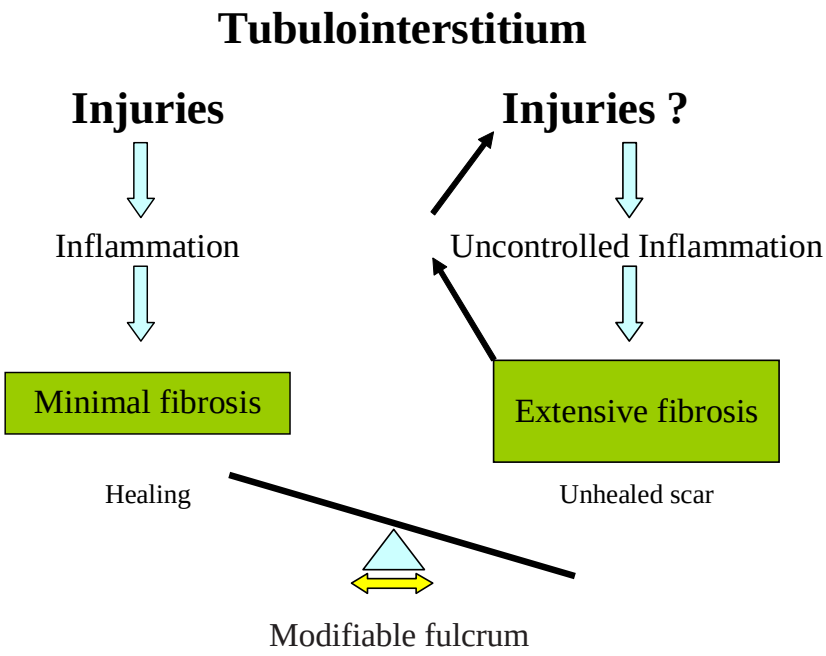

Fig. 2 The healing and the damaging pathways in the kidney. Both share common mechanisms but to a different degree. Current experimental data suggest the presence of unravelling injuries that continuously persist thus setting the fulcrum toward tissue damage.

progression may be nothing else but the chronic activation of the renin angiotensin system. Fioretto et al demonstrated some degree of reversibility of glomerular structure in diabetic nephropathy patients at year 5 after receiving pancreatic transplantation [98]. Recently, this group showed, a 10-year follow-up of renal histology which revealed obvious improvement of tubulointerstititial lesions. This confirmed that chronic renal scarring might regress if the real pathogenic insults have been eliminated long enough [99].

Conclusion

Irrespective of the primary causes, kidneys actively progress toward end-stage renal disease in a similar pattern. Current data indicate common mechanisms of progression. Many of these are common repairing mechanisms. This suggests that the kidney does not sentence itself to death but tries to balance between healing and harm (**Fig. 2**). Henceforth, the fulcrum of this balance remains to be elucidated but several data suggest that it should be located in close proximity to the activation site of the renin angiotensin system.

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References

1. Klahr S. Progression of chronic renal disease. Heart Dis. 2001;3:205-9.
2. Henle J, Pfeufer C, Bright M. Klinische Mitteilungen. Z Rationelle Med Zurich. 1844; 1:1844.
3. Chanutin A, Ferris EB. Experimental renal insufficiency produced by partial nephrectomy.1. Control diet. Arch. Intern. Med. 1932;49:767-87.
4. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potential adverse response to renal abrasion. Am J Physiol. 1981;241: F85-93.
5. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int.1996;49:1774-77.
6. Strutz F, Mueller G. Mechanism of renal fibrogenesis. In: Nelson EG, Couser WG. editor. Immunologic Renal Disease (2nd ed). Lippincott and Wilkins: Philadelphia. USA; 2001. p. 73-104.
7. Chatziantoniou C, Dussaule JD. Insights into the mechanisms of renal fibrosis: is it possible to achieve regression? Am J Physiol. 2005;289: F227-34.
8. Liu Y. Renal fibrosis: new insights into the pathogenesis and therapeutics. Kidney Int. 2006;69: 213-7.
9. Wolf G, Neilson EG. Angiotensin II as a renal growth

factor. J Am Soc Nephrol.1993;3:1531-40.
10. Salehmoghaddam S, Bradley T, Mikhail N, Badie-Dezfooly B, Nord EP, Trizna W, et al. Hypertrophy of basolateral Na-K pump activity in the proximal tubule of the remnant kidney. Lab Invest. 1985;53:443-52.
11. Lotspeich WD. Renal hypertrophy in metabolic acidosis and its relation to ammonia excretion. Am J Physiol. 1965;208:1135-42.
12. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulointerstitital disease in rats. Interaction of dietary acid load, ammonia and complement component C3. J Clin Invest. 1985;76: 667-75.
13. Oliver J. Architecture of the kidney in chronic Bright's disease. New York:Hoeber, 1939.
14. Remuzzi G, Bertani T. Is glomerulosclerosis a consequence of altered glomerular permeability of macromolecules? Kidney Int. 1990;38:384-94.
15. Oliver J, Macdowell M, Lee YC. Cellular mechanisms of protein metabolism in the nephron. I. The structural aspects of proteinuria; tubular absorption, droplet formation, and the disposal of proteins. J Exp Med. 1954;99:589-604.
16. Mezzano SA, Barria M, Droguett MA, Burgos ME, Ardiles LG, Flores C, Egido J. Tubular NF-kappaB and AP-1 activation in human proteinuric renal disease. Kidney Int. 2001;60:1366-77.
17. Burton CJ, Combe C, Walls J, Harris KP. Secretion of chemokines and cytokines by human tubular epithelial cells in response to protein. Nephrol Dial Transplant. 1999;14:2628-33.
18. Kikuchi H, Kawachi H, Ito Y, Matsui K, Nosaka H, Saito A, et al. Severe proteinuria, sustained for 6 months, induces tubular epithelial cell injury and cell infiltration in rats but not progressive interstitial fibrosis. Nephrol Dial Transplant. 2000;15:799-810.
19. Okuda S, Oochi N, Wakisaka M, Kanai H, Tamaki K, Nagase S, et al. Albuminuria is not an aggravating factor in experimental focal glomerulosclerosis and hyalinosis. J Lab Clin Med.1992;245-53.
20. Arici M, Chana R, Lewington A, Brown J, Brunskill NJ. Stimulation of proximal tubular cell apoptosis by albumin-bound fatty acids mediated by peroxisome proliferator activated receptor-gamma. J Am Soc Nephrol. 2003;14:17-27.
21. Tang S, Leung JC, Tsang AW, Lan HY, Chan TM, Lai KN. Transferrin up-regulates chemokine synthesis by human proximal tubular epithelial cells: implication on mechanism of tubuloglomerular communication in glomerulopathic proteinuria. Kidney Int. 2002;61: 1655-65.
22. Cases A, Coll E. Dyslipidemia and the progression of renal disease in chronic renal failure patients.Kidney Int. 2005;99 (Suppl 1): S87-93.
23. Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, et al. Predictors of the progression of renal disease in the modification of diet in renal disease study. Kidney Int. 1997;51:1908-19.
24. Eddy AA. Interstitial fibrosis in hypercholesterolemic rats: role of oxidation, matrix synthesis, and proteolytic cascades. Kidney Int. 1998;53:1182-9.
25. Harada K, Akai Y, Kurumatani N, Iwano M, Saito Y. Prognostic value of urinary interleukin 6 in patients with IgA nephropathy: an 8-year follow-up study. Nephron. 2002; 92:824-6.
26. Nangaku M. Complement regulatory proteins in glomerular diseases. Kidney Int. 1998; 54:1419-28.
27. Hsu SI, Couser WG. Chronic progression of tubulointerstitial damage in proteinuric renal disease is mediated by complement activation: a therapeutic role for complement inhibitors? J Am Soc Nephrol. 2003;14 (Suppl.2): S186-91.
28. Matsuo S, Ichida S, Takizawa H, Okada N, Baranyi L, Iguchi A, et al. In vivo effects of monoclonal antibodies which functionally inhibit complement regulatory proteins in rats. J Exp Med. 1994;180:1619-27.
29. Nomura A, Morita Y, Maruyama S, Hotta N, Nadai M, Wang L, et al. Role of complement in acute tubulointerstitial injury of rats with aminonucleoside nephrosis. Am J Pathol. 1997;151:539-47.
30. Nangaku M, Pippin J, Couser WG. C6 mediates chronic progression of tubulointerstitial damage in rats with remnant kidneys. J Am Soc Nephrol. 2002;13:928-36
31. Gerritsma JS, Gerritsen AF, De Ley M, van Es LA, Daha MR. Interferon-gamma induces biosynthesis of complement components C2, C4 and factor H by human proximal tubular epithelial cells. Cytokine. 1997; 9:276-83.
32. Hostetter MK, Johnson GM. The erythrocyte as instigator of inflammation. Generation of amidated C3 by erythrocyte adenosine deaminase. J Clin Invest. 1989;84:665-71.
33. Manotham K, Tanaka T, Matsumoto M, Ohse T, Miyata T, Inagi R, et al. Evidence of tubular hypoxia in the early phase in the remnant kidney model. J Am Soc Nephrol. 2004;15:1277-88.
34. Matsumoto M, Tanaka T, Yamamoto T, Noiri E, Miyata T, Inagi R, et al. Hypoperfusion of peritubular capillaries induces chronic hypoxia before progression of tubulointerstitial injury in a progressive model of

rat glomerulonephritis. J Am Soc Nephrol. 2004;15: 1574-81.
35. Corpechot C, Barbu V, Wendum D, Kinnman N, Rey C, Poupon R, et al. Hypoxia-induced VEGF and collagen I expressions are associated with angiogenesis and fibrogenesis in experimental cirrhosis. Hepatology. 2002;35:1010-21.
36. Combe C, Burton CJ, Dufourco P, Weston S, Horsburgh T, Walls J, et al. Hypoxia induces intercellular adhesion molecule-1 on cultured human tubular cells. Kidney Int. 1997;51:1703-9.
37. Hampel DJ, Sansome C, Romanov VI, Kowalski AJ, Denhardt DT, Goligorsky MS. Osteopontin traffic in hypoxic renal epithelial cells. Nephron Exp Nephrol. 2003;94:66-74.
38. Norman JT, Clark IM, Garcia P. Hypoxia promotes fibrogenesis in human renal fibroblast. Kidney Int. 2000;58: 2351-66.
39. Manotham K, Tanaka T, Matsumoto M, Ohse T, Inagi R, Miyata T, et al. Transdifferentiation of cultured tubular cells induced by hypoxia. Kidney Int. 2004; 65:871-80.
40. Ohashi R, Shimizu A, Masuda Y, Kitamura H, Ishizaki M, Sugisaki Y, et al. Peritubular capillary regression during the progression of experimental obstructive nephropathy. J Am Soc Nephrol. 2002;13:1795-805.
41. Bohle A, M ller GA, Wehrmann M, Mackensen-Haen S, Xiao JC. Pathogenesis of chronic renal failure in the primary glomerulopathies, renal vasculopathies, and chronic interstitial nephritides. Kidney Int. 1996; 49(Suppl.1):S2-9
42. Eddy A. Role of cellular infiltrates in response to proteinuria. Am J Kidney Dis. 2001; Suppl 2: S25-9.
43. Donadelli R, Zanchi C, Morigi M, Buelli S, Batani C, Tomasoni S. Protein overload induces fractalkine upregulation in proximal tubular cells through nuclear factor kappaB- and p38 mitogen-activated protein kinase-dependent pathways. J Am Soc Nephrol. 2003; 14:2436-46.
44. Tu Z, Kelley VR, Collins T, Lee FS. I kappa B kinase is critical for TNF-alpha-induced VCAM1 gene expression in renal tubular epithelial cells. J Immunol. 2001;166:6839-46.
45. Fan JM, Huang XR, Ng YY, Nikolic-Paterson DJ, Mu W, Atkins RC, et al.Interleukin-1 induces tubular epithelial-myofibroblast transdifferentiation through a transforming growth factor-beta1-dependent mechanism in vitro. Am J Kidney Dis. 2001;37:820-31.
46. Guo G, Morrissey J, McCracken R, Tolley T, Klahr S. Role of TNFR1 and TNFR2 receptors in tubulointerstitial fibrosis of obstructive nephropathy. Am J Physiol Renal Physiol. 1999;277: F766-72.
47. Guo G, Morrissey J, McCracken R, Tolley T, Liapis H, Klahr S. Contributions of angiotensin II and tumor necrosis factor to the development of renal fibrosis. Am J Physiol Renal Physiol. 280:F777-85.
48. Lan HY, Nikolic-Paterson DJ, Mu W, Vannice JL, Atkins RC. Interleukin-1 receptor antagonist halts the progression of established glomerulonephritis in the rat. Kidney Int. 1995;47:1303-09.
49. Vesey DA, Cheung CW, Cuttle L, Endre ZA, Gob G, Johnson DW. Interleukin-1beta induces human proximal tubule cell injury, alpha-smooth muscle actin expression and fibronectin production. Kidney Int. 2002;62:31-40.
50. Fukatsu A, Matsuo S, Yuzawa Y, Miyai H, Futenma A, Kato K. Expression of inteleukin-6 and major histocompatibility complex molecules in tubular epithelial cells of diseased human kidney. Lab Invest. 1993;69:58-6.
51. Taal MW, Omer SA, Nadim MK, Mackenzie HS. Cellular and molecular mediators in common pathway mechanisms of chronic renal disease progression. Curr Opin Nephrol Hypertens. 2000;9:323-31.
52. Viedt C, Orth SR. Monocyte chemoattractant protein-1 (MCP-1) in the kidney: does it more than simply attract monocytes? Nephrol Dial Transplant. 2002; 17:2043-7.
53. Tesch GH, Schwarting A, Kinoshita K, Lan HY, Rollins BJ, Kelley VR. Monocyte chemoattractant protein-1 promotes macrophage-mediated tubular injury, but not glomerular injury, in nephrotoxic serum nephritis. J Clin Invest. 1999;103:73-80.
54. Ruiz-Ortega M, Rup rez M, Esteban V, Rodr guez-Vita J, S nchez-L pez E, Carvajal G, et al. Angiotensin II: a key factor in the inflammatory and fibrotic response in kidney diseases. Nephrol Dial Transplant. 2006;21: 16-20.
55. Wolf G, Hannken T, Burns K, Harris R, Stahal RAK, Thaiss T. Angiotensin II activates the NF-kB pathway through AT2-receptors. J Am Soc Nephrol. 2000;11: 430A (Abstract).
56. Naruse T, Yuzawa Y, Akahori T, Mizuno M, Maruyama S, Kannagi R, et al. P-selectin-dependent macrophage migration into the tubulointerstitium in unilateral ureteral obstruction. Kidney Int. 2002;62:94-105.
57. Sean Eardley K, Cockwell P. Macrophages and progressive tubulointerstitial disease. Kidney Int. 2005;68:437-55.
58. Nakamura K, Oka M, Shirai M, Igarashi Y, Kojima K,

Kaneko O, et al. Source of reactive oxygen species in anti-Thy1 nephritis. Ren Fail. 1998;20:399-405.
59. Ogawa D, Shikata K, Honke K, Sato S, Matsuda M, Nagase R, et al. Cerebroside sulfotransferase deficiency ameliorates L-selectin-dependent monocyte infiltration in the kidney after ureteral obstruction. J Biol Chem. 2004;279:2085-90.
60. Diamond JR, Pesek I, Ruggieri S, Karnovsky MJ. Essential fatty acid deficiency during acute puromycin nephrosis ameliorates late renal injury. Am J Physiol. 1989;257:F798-807.
61. Stout RD, Jiang C, Matta B, Tietzel I, Watkins SK, Suttles J. Macrophages sequentially change their functional phenotype in response to changes in microenvironmental influences. J Immunol. 2005;175: 342-9.
62. Friedman SL. Mac the knife? Macrophages - the double-edged sword of hepatic fibrosis. J Clin Invest. 2005;115:29-32.
63. Duffield JS, Tipping PG, Kipari T, Cailhier JF, Clay S, Lang R, et al. Conditional ablation of macrophages halts progression of crescentic glomerulonephritis. Am J Pathol 2005;167:1207-19.
64. Rodr guez-Iturbe B, Pons H, Herrera-Acosta J, Johnson RJ. Role of immunocompetent cells in non-immune renal diseases. Kidney Int. 2001;59:1626-40.
65. Weiss RA, Madaio MP, Tomaszewski JE, Kelly CJ. T cells reactive to an inducible heat shock protein induced disease in toxin-induced interstitial nephritis. J Exp Med. 1994;180:2239-50.
66. Panzer U, Steinmetz OM, Reinking RR, Meyer TN, Fehr S, Schneider A, et al. Compartment-specific expression and function of the chemokine IP-10/ CXCL10 in a model of renal endothelial microvascular injury. J. Am Soc Nephrol. 2006;17:454-64.
67. Avihingsanon Y, Phumesin P, Benjachat T, Akkasilpa S, Kittikowit V, Praditpornsilpa K, et al. Measurement of urinary chemokine and growth factor messenger RNAs: a noninvasive monitoring in lupus nephritis. Kidney Int. 2006;69:747-53.
68. Fujihara CK, Noronha IL, Malheiros, Antunes GR, de Oliveira IB, Zatz R. Combined mycophenolate mofetil and losartan therapy arrests established injury in the remnant kidney. J Am Soc Nephrol. 2000;11:283-90.
69. Border WA, Noble NA,Yamamoto T, Harper JR, Yamaguchi Y, Pierschbacher MD, et al. Natural inhibitor of transforming growth factor protects against scarring in experimental kidney disease. Nature.1992;360:361-4.
70. Okada H, Kikuta T, Kobayashi T, Inoue T, Kanno Y, Takigawa M, et al. Connective tissue growth factor expressed in tubular epithelium plays a pivotal role in renal fibrogenesis. J Am Soc Nephrol. 2005;16:133-43.
71. Bottinger EP, Bitzer M. TGF-beta signaling in renal disease. J Am Soc Nephrol. 2002;13:2600-10.
72. Wolf G, Ziyadeh FN, Zahner G, Stahl RA. Angiotensin II-stimulated expression of transforming growth factor beta in renal proximal tubular cells: attenuation after stable transfection with the c-mas oncogene. Kidney Int. 1995;48:1818-27.
73. Ziyadeh FN. Mediators of diabetic renal disease: the case for TGF-beta as the major mediator. J Am Soc Nephrol. 2004;15(Suppl 1):S55-7.
74. Oldroyd SD, Thomas GL, Gabbiani G, El Nahas AM. Interferon-gamma inhibits experimental renal fibrosis. Kidney Int. 1999;56:2116-27.
75. Gong R, Rifai A, Tolbert EM, Biswas P, Centracchio JN, Dworkin LD. Hepatocyte growth factor ameliorates renal interstitial inflammation in rat remnant kidney by modulating tubular expression of macrophage chemoattractant protein-1 and RANTES. J Am Soc Nephrol. 2004;15:2868-81.
76. Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, et al. BMP-7 counteracts TGF-beta1-induced epithelial to mesenchymal transition and reverses chronic renal injury. Nat Med. 2003;9:964-8.
77. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. J Clin Invest. 2003;111:707-16.
78. Iwano M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. Curr Opin Nephrol Hypertens. 2004;13: 279-84.
79. Zeisberg M, Strutz F, Muller GA. Renal fibrosis: an update. Curr Opin Nephrol Hypertens. 2001;10: 315-20.
80. Ng YY, Huang TP, Yang WC, Chen ZP, Yang AH, Mu W, et al. Tubular epithelial-myofibroblast transdifferentiation in progressive tubulointerstitial fibrosis in 5/6 nephrectomized rats. Kidney Int. 1998; 54:864-76.
81. Li JH, Wang W, Huang XR, Oldfield M, Schmidt AM, Cooper ME, et al. Advanced glycation end products induce tubular epithelial-myofibroblast transition through the RAGE-ERK1/2 MAP kinase signaling pathway. Am J Pathol. 2004; 164:1389-97.
82. Yang J, Dai C, Liu Y. A novel mechanism by which hepatocyte growth factor blocks tubular epithelial to mesenchymal transition. J Am Soc Nephrol. 2005;16:

68-78.
83. Okada H, Danoff TM, Kalluri R, Neilson EG. Early role of Fsp1 in epithelial-mesenchymal transformation. Am J Physiol. 1997;273:F563-74.
84. Eddy AA Plasminogen activator inhibitor-1 and the kidney. Am J Physiol Renal Physiol. 2002;283: F209-20.
85. Kim H, Oda T, Lopez-Guisa J, Wing D, Edwards DR, Soloway PD, Eddy AA. TIMP-1 deficiency does not attenuate interstitial fibrosis in obstructive nephropathy. J Am Soc Nephrol. 2001;12:736-48.
86. Oda T, Jung YO, Kim HS, Cai X, L pez-Guisa JM, Ikeda Y, et al. PAI-1 deficiency attenuates the fibrogenic response to ureteral obstruction. Kidney Int. 2001; 30:587-96.
87. Ruggenenti P, Schieppati A, Remuzzi G. Progression, remission, regression of chronic renal diseases. Lancet. 2001;357:1601-8.
88. Elger M, Hentschel H, Litteral J, Wellner M, Kirsch T, Luft FC, et al. Nephrogenesis is induced by partial nephretomy in the elasmorbrach Leucoraja enricea. J Am Soc Nephrol. 2003;14:1506-18.
89. Villanueva S, Cespedes C, Vio CP. Ischemic acute renal failure induces the expression of a wide range of nephrogenic proteins. Am J Physiol. 2006;29:R861-70.
90. Morigi M, Imberti B, Zoja C, Corna D, Tomasoni S, Abbate M, et al. Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. J Am Soc Nephrol. 2004; 15:1794-804.
91. Duffield JS, Park KM, Hsiao LL, Kelley VR, Scadden DT, Ichimura T, et al. Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. J Clin Invest. 2005;115:1743-55.
92. Bussolati B, Bruno S, Grange C, Buttiglieri S, Deregibus MC, Cantino D, et al. Isolation of renal progenitor cells from adult human kidney. Am J Pathol. 2005;166:545-55.
93. Shankland SJ, Eitner F, Hudkins KL, Goodpaster T, D'Agati V, Alpers CE. Differential expression of cyclin-dependent kinase inhibitors in human glomerular disease: role in podocyte proliferation and maturation. Kidney Int. 2000;58:674-83.
94. Nelson PJ, Gelman IH, Klotman PE. Suppression of HIV-1 expression by inhibitors of cyclin-dependent kinases promotes differentiation of infected podocytes. J Am Soc Nephrol. 2001;12:2827-31.
95. Adamczak M, Gross ML, Krtil J, Koch A, Tyralla K, Amann K, et al. Reversal of glomerulosclerosis after high-dose enalapril treatment in subtotal nephrectomized rats. J Am Soc Nephrol. 2003;14: 2833-42.
96. Fujihara CK, Velho M, Malheiros DM, Zatz R. An extremely high dose of losartan affords superior renoprotection in the remnant kidney model. Kidney Int. 2005;67:1913-24.
97. Koo JW, Kim Y, Rozen S, Mauer M. Enalapril accelerates remodeling of the renal interstitium after release of unilateral ureteral obstruction in rats. J Nephrol. 2003;16:203-9.
98. Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med. 1998; 339:69-75.
99. Fioretto P, Sutherland DE, Najafian B, Mauer M. Remodeling of renal interstitial and tubular lesions in pancreas transplant recipients. Kidney Int. 2006;69: 907-12.