Published in final edited form as:

Pediatr Nephrol. 2010 November ; 25(11): 2223–2230. doi:10.1007/s00467-010-1503-4.

A conceptual framework for the molecular pathogenesis of progressive kidney disease

H. William Schnaper,

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

Susan C. Hubchak,

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

Constance E. Runyan,

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

James A. Browne,

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

Gal Finer,

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

Xiaoying Liu, and

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

Tomoko Hayashida

Division of Kidney Diseases, Department of Pediatrics, Feinberg School of Medicine,
Northwestern University, Chicago, IL, USA
Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, IL 60614-3363, USA

Abstract

The data regarding the pathogenesis of progressive kidney disease implicate cytokine effects, physiological factors, and myriad examples of relatively nonspecific cellular dysfunction. The sheer volume of information being generated on this topic threatens to overwhelm our efforts to

understand progression in chronic kidney disease or to derive rational strategies to treat it. Here, a conceptual framework is offered for organizing and considering these data. Disease is initiated by an injury that evokes a tissue-specific cellular response. Subsequent structural repair may be effective, or the new structure may be sufficiently changed that it requires an adaptive physiological response. If this adaptation is not successful, subsequent cycles of misdirected repair or maladaptation may lead to progressive nephron loss. To illustrate how this framework can be used to organize our approach to disease pathogenesis, the role of cytokines in proteinuria and progressive glomerular disease is discussed. Finally, this theoretical framework is reconsidered to examine its implications for the diagnosis and treatment of clinical conditions. Application of this schema could have significant relevance to both research inquiry and clinical practice.

Keywords

Chronic kidney disease; Fibrosis; Kidney; Signal transduction

Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by scarring and loss of structural integrity of the kidney. It has been estimated to affect more than 26 million people in the USA alone [1]. Although it has been suggested that this number may represent an overestimation [2], the attendant morbidity, mortality, and financial costs clearly are significant. Despite its frequency and impact, advances in preventing CKD remain limited. In part, this reflects our inability to identify critical biological targets for treatment. Over the past few years, a tremendous amount of data has been generated, and an even greater amount of interpretation has been offered, as we seek to understand the molecular pathogenesis of progression. Experimental studies to define the evolution from an initial lesion to the common pathway of CKD have employed two, very different techniques. In a traditional approach involving molecular analysis of signal transduction pathways, cell phenotypic markers and synthetic activity have been used to characterize mechanisms leading to loss of structural integrity of the cell, extracellular matrix (ECM) accumulation, or disordered organ structure. In a second approach, the ability to manipulate the genetic constitution of animals has led to transgenic and knockout models, especially in mice. There are positive and negative attributes to either approach. The iterative, pathway-based inquiry offers precise details of the fine specificity of cell regulation, with clear indications of how each molecule participates in the events being studied. However, while the painstaking analysis of such events (by investigators including these authors) provides reams of data, the likelihood is small that an isolated, individual change at a cellular level causes CKD. The pathology may initiate with a single event but, quickly thereafter, a multitude of pathways are activated to cause what we would recognize as the disease. Conversely, in animals where a gene has been modified or deleted, it is difficult to be confident that the gene being manipulated represents the true “first cause” of the disease process. The exception to this assertion is, of course, monogenic disorders wherein an identified mutation has been “knocked in” in mice, to model the human disease. Even in this case, however, potential differences of interspecies physiology introduce a degree of uncertainty into our extrapolating from the model to

humans. Further, the identity of the involved gene reveals only a single step in a complex causal cascade.

As a result, we frequently find that a protein has been implicated as *the* cause of a disease or a pathogenetic event, when it is simply a possible cause or contributing agent. How can we understand the multiple factors that contribute to disease? In this essay, rather than providing a comprehensive review of the research findings in CKD, we will seek to provide a framework for fitting these varied findings into an overall schema for the pathogenesis of progressive renal scarring. This approach should help us understand the part that each finding plays in the overall pathway.

First iteration: stages involved in disease pathogenesis

In considering how disease occurs, a basic tenet is that there is no such thing as a truly isolated “pathogenic mechanism”. Every event and response of the organism has developed through evolution in order to enhance the continuation of the species. Disease occurs when an otherwise physiological response is misapplied, causing a loss of function or an imbalanced response. For example, our ability to utilize tubuloglomerular feedback in order to adapt to acute tubular injury shuts off glomerular filtration to prevent death from acute fluid loss and shock [3], but risks harm from fluid overload or hyperkalemia. More chronically, a process for the healing of vascular intimal injury may be misapplied, causing the development of atherosclerosis [4]. Later in this review, we will consider that tubuloglomerular feedback, through a chronic mechanism, may contribute to progressive renal fibrosis.

A four-step process is common to all cases of chronic renal disease. An initial stimulus causes *injury*. The subsequent cellular *response* initiates *repair* mechanisms that may be appropriate or may be misapplied or inappropriately regulated. Even if the repair is successful, the organism must accommodate to any structural changes resulting from the repair. This *adaptation* may lead to a return to the previous steady state, or it may alter physiology sufficiently that the nephron is stressed. Extended effects of such adaptation may be deleterious for the organism, causing what we recognize as disease. These four stages are the subject of the present essay.

In an earlier generation, this relationship among injury, response, and potential untoward outcomes was described at the level of systemic physiology in Bricker’s seminal description of the pathophysiology of the uremic state [5]. Today, the application of a similar paradigm to that proposed by Bricker, but at a molecular level, may help us understand the abnormal structure/function correlates of progressive kidney disease (Fig. 1). An *injury* initiates this process. The term is used broadly here; an injury may be an event, such as an infection, hypoxic insult, or exposure to a toxin. But it also could represent a physiological stress, such as that caused by glomerular overload in obesity. A genetically inherited disorder may cause a structural defect, activating compensatory mechanisms that similarly cause physical stress to the nephron.

An initial response to this injury involves the activation of cellular mechanisms, such as further inflammation, the production of proteases, and changes in cell function (e.g. a switch from the transport to synthetic phenotype). Mediators are produced to propagate this response in an ever-widening circle. Cells proliferate, or they may die (apoptosis or necrosis). The specificity involved in the initial injurious stimulus may become obscured, as responses begin to enter several common pathways. A final common pathway is reached when the *repair process* is initiated. New basement membranes are synthesized, beginning with a provisional ECM, such as fibronectin [6], but eventually including different types of collagen and laminin that are more specific to a given structure. Angiogenesis may establish a new capillary bed, and cells of all types proliferate and ultimately differentiate into specific structures, such as capillary endothelia or renal tubules, among others. Regulation of these repair mechanisms is a critical determinant of outcome. If the steps described here are successful, and the repair process terminates when an effective structure is re-established, normal physiology is restored and health is reconstituted. However, if the response is insufficient, normal structures are not present. Further, if the response is excessive (e.g. if the ECM-producing response is not shut off), scarring may interfere with function. If the damage is limited, the organism can *adapt*, and a *new steady state* may be achieved, with perhaps a bit less function than previously. However, it is often the case that the effort of adaptation itself represents *abnormal physiology*. Overload of the remaining nephrons from compensatory mechanisms creates a vicious cycle of injury and unsuccessful repair. The result is chronic disease and progressive nephron loss.

Illustration: role of cytokines in proteinuria and progression

Let us examine an example of how this model of pathogenesis may be applied. Cytokines have been implicated in both proteinuria and subsequent progressive chronic kidney failure. The different roles played by these proteins in minimal change disease (MCD) and idiopathic focal segmental glomerulosclerosis (FSGS) illustrate our conceptual framework. It is important to note that this is offered as a single example. Cytokines are not the only mediators of proteinuria or progressive disease, and the initial lesion in progressive disease may arise in the tubule rather than in the glomerulus.

Injury and response in the pathogenesis of MCD

Since Shalhoub first proposed that MCD is a T-lymphocyte disorder [7], investigators have sought an immunological factor (cytokine) that mediates the disease [8]. Despite ample molecular evidence of a role for lymphocytes in this disorder [9], a definitive role for cytokines remains an elusive target [10]. Interleukin (IL)-13 has been suggested as a potential mediator of MCD [11]. Other cytokines have been identified as potential stimuli of proteinuria in MCD, including vascular endothelial cell growth factor (VEGF), formerly called vascular permeability factor [12], and IL-8 [13]. VEGF seems to be a likely candidate inducer of glomerular proteinuria, since it causes cytoskeletal rearrangement [14] that would alter the structure of the slit diaphragm and may be responsible for proteinuria in diabetic nephropathy [15]. It is likely that cytoskeletal reorganization in the podocyte [16] alters the slit diaphragm in a way that permits increased macromolecular clearance. Viewed according to the model depicted in Fig. 1, the *initial injury* in MCD could be seen as resulting in some

way from disordered T-cell function. The *cellular response* might be VEGF production, cytoskeletal rearrangement, and mislocalization of proteins that regulate cell–cell and cell–matrix interactions [11, 17]. Consequent changes in the slit diaphragm enhance the passage of macromolecules. These events would represent a potential triggering injury and the initial cellular response to that injury (Fig. 2, left-hand side of figure). In most cases of MCD, this represents a reversible, self-limiting process. Indeed, the reversibility of MCD could be explained by the transient nature of the cytoskeletal rearrangement, which might not even invoke a repair mechanism.

Repair: the distinct cytokine profile in progressive glomerular disease

None of the cytokines mentioned to this point, including VEGF, have been associated with the cell loss and ECM accumulation observed in CKD. Yet, proteinuria is often considered to be associated with progressive nephron loss. Since MCD rarely, if ever, undergoes progression, there must be something different about the mechanisms underlying proteinuria in idiopathic FSGS (compare [18]) that is important for causing CKD. In FSGS, the nature of the injury and initial response generates a second wave of cytokines (right-hand side of Fig. 2). These cytokines may be beneficial, promoting a repair process in which damaged glomerular and tubular structures are replaced by cell dedifferentiation, migration, proliferation, and redifferentiation. Transforming growth factor beta (TGF- β) stimulates podocyte apoptosis [19] and mesangial cell ECM production [20], and where tubular damage occurs, tubular cells are induced to dedifferentiate by TGF- β and other cytokines [21]. Although often felt to be a pathogenic event, apoptosis might also serve a regulatory purpose in helping to remove damaged or activated cells to regulate repair [22]. Macrophage chemoattractant protein (MCP)-1, basic fibroblast growth factor (FGF-2), and platelet-derived growth factor (PDGF) serve as chemoattractants to recruit and stimulate the proliferation of macrophages to remove cellular debris, stem cells to promote repair, endothelial cells to produce new blood vessels, or fibroblasts to lay down new ECM.

Misdirected repair in overt FSGS and its progression to CKD

Ideally, the kidney undergoes successful *adaptation* to this injury and repair, re-establishing normal or near-normal function. However, at some point, if it is not tightly regulated, the repair process may become disproportionate (right-hand part of Fig. 2). Apoptosis or necrosis may destroy vital structures, and infiltrating cells may release further waves of cytokines or produce excess or inappropriate ECM. Although to this point we have focused on glomerular disease, by this time the lesion has become more diffuse. The entire kidney becomes affected by the mechanisms that have been activated, a process manifesting as the final common pathway of CKD. Repair-directed cytokines continue to play a significant part. TGF- β has been implicated in progressive nephron loss [21, 23, 24], along with other cytokines that either are downstream of TGF- β or act independently, including leptin [25], connective tissue growth factor (CTGF) [26], and osteonectin [27]. Some of these cytokines may be found in the urine of patients with fibrotic kidney disease [28]. Other mediators also may contribute to progression. Tumor necrosis factor alpha (TNF- α) [29], osteopontin [30], and MCP-1 [31] have been associated with inflammatory components of progression, and FGF-2 [32], epidermal growth factor (EGF) [33], and PDGF [34] activate and amplify cellular activities in CKD. PAI-1, a multifunctional molecule that originally was defined by

its procoagulant activity, has multiple effects along these pathways that regulate progressive scarring [35]. Significantly, there appears to be little overlap between this group of “repair” cytokines and those causing proteinuria. For example, diabetic mice that are lacking the TGF- β signaling molecule, Smad3, develop significant proteinuria but show decreased fibrosis [36].

Uncontrolled, this second wave of cytokines may promote renal scarring. Sufficiently excessive, misdirected repair invokes an adverse adaptation in an effort to maintain glomerular filtration rate (GFR) as compensation for the overwhelming injury. Nephron loss leads to functional overload of the remaining nephrons. Tubuloglomerular feedback elevates single-nephron GFR in a complex mechanism dependent at least in part on angiotensin [37]. Angiotensin II, an important contributor to this feedback, also plays a central role in hypertension, hypertrophy, and the activation of other cytokine pathways [38]. Hypertrophy, in turn, further stimulates the production of mediators that, at appropriate concentrations, engender repair, but which under pathological conditions amplify or accelerate the fibrotic process. Given that this adaptation provokes further injury, we refer to it here as “maladaptation”. With these events, the lesion has reached the “tipping point” of the fibrogenic cascade, and the process becomes irreversible. The result is chronic, progressive kidney scarring. Thus, the initial injury has stimulated a cellular response, dysregulated repair, maladaptation, and a spiral of progressive nephron loss.

Non-cytokine mechanisms

Although we have focused on cytokine production as one mediator of glomerulosclerosis that becomes amplified to cause generalized nephron loss, other mediators show similar patterns. For example, reactive oxygen species, such as nitric oxide (NO), play an important role in determining renal hemodynamics in health and disease [39], yet they could be a mediator of maladaptive glomerular hypertrophy [40] and, derived from multiple cell types, a mediator of fibrosis [41]. Kriz has proposed a model in which misdirected filtration of plasma proteins into the tubulointerstitial space stimulates a reactive process that could conceivably repair the lesion but eventually chokes off tubular flow, impairing glomerular filtration and leading to nephron loss [42]. In diseases arising from primary tubular dysfunction, maladaptive responses similarly lead to nephron loss. In these examples, as with our discussion of FSGS, normally beneficial mechanisms are misapplied. To benefit from this insight, we must perform two critical tasks in dissecting the pathogenesis of CKD. The first requires us to understand the elements of the disease process that initiate repair and how some diseases, such as MCD, or disease models, such as single-dose, rat anti-Thy1 nephritis [43], appear to be self-limited, whereas others, such as idiopathic FSGS and the multi-dose model of anti-Thy1 nephritis, provoke repair mechanisms that may be misdirected. The second task is to determine how the focus and extent of repair mechanisms are regulated.

Genetic influences on manifestations of the model

One critical parameter controlling repair may be genetic predisposition. While our proposed theoretical construct may seem relatively straightforward, its application to clinical disease

is complicated. Many of us are exposed regularly to pathogenic stimuli, yet only a small number of us, in some defined instances, actually develop disease. Thus, it is reasonable to conjecture that specific genetic polymorphisms may play a role in the pathogenesis of various kidney diseases by increasing the activity or expression of angiotensin-converting enzyme (ACE) [44], MCP-1 [45], or TGF- β [46]. Further, it is known that children with certain extended HLA haplotypes are predisposed to developing frequently relapsing MCD [47], and specific genes now have been associated with glomerulosclerosis [48]. Examples of FSGS that are associated with Mendelian inheritance may represent only the “tip of the iceberg” with regard to the genetic basis for the lesion. Allelic variants in podocyte-specific structure or function genes may not be readily apparent but could predispose patients to an unfavorable initial response, altering the balance between appropriate and inappropriate repair to promote progressive nephron loss. Thus, a critical aspect of the initial response may be a genetic predisposition to respond inappropriately to injury (Fig. 3). Under a requisite set of genetic influences, the initiating stimuli of infection/inflammation, stress/structural overload, toxin, among others, will generate a cell response that manifests as the initial lesion, whereas individuals without the “proper” alleles may not develop any disease.

Reiteration of the model: relevance to diagnosis and treatment

In the clinical context, where the primary disease stimulus will be less apparent than in controlled animal experiments, we may not have sufficient tools to differentiate between processes that represent the initial damage caused by the *injury* and those that reflect the tissue *response* to that injury. Thus, the two stages are linked in the clinical schema shown in Fig. 3. We propose that initiation of the lesion is followed by a phase of disease consolidation, which corresponds to the reversible stage of the repair process—in our previous example, early FSGS. Influencing factors, such as nephron number, hypertension, and the possible presence of nephron overload [47], will determine whether the patient can successfully adapt to the physiological alterations consequent upon the development of glomerulosclerosis. This time of consolidation represents the stage at which the clinician often first encounters the patient, wherein all therapies should be directed toward modulating the *repair* process so it is appropriately directed and limited in scope. Once podocyte and other glomerular cell hypertrophy ensues, FSGS is overt and relatively resistant to traditional glomerular disease treatment. Nephron loss creates conditions of increased single-nephron load, accelerating the organism’s efforts at repair that are doomed to advance the fibrotic process. As the protein reabsorptive mechanisms of the tubule are saturated, further inflammatory responses promote tubulointerstitial fibrosis [49]. Loss of vasculature from inflammation or other mechanisms leads to tissue hypoxia, further stressing the tissue and inducing more apoptosis. This *maladaptation* leads to further injury and is likely to be enhanced by “progression genes” such as MYH9 [48] in ways that we do not fully understand. Possible contributing factors that could be genetically modified include excessive cytokine responses, enhanced ECM synthesis or reduced ECM protease production, or the generation of reactive oxygen species, including oxidized lipids. All of these represent the inappropriate activation of repair mechanisms.

Implications for clinical care

Thus, the framework described in the first part of this essay can be used to describe the pathogenesis of a specific disease, in this case, idiopathic FSGS leading to CKD. Others can undoubtedly construct similar scenarios regarding diseases that originate in the tubulointerstitium, such as chronic pyelonephritis or polycystic kidney disease. The important questions are: (1) how can we utilize this approach to help us understand the pathogenesis of clinical disease? and (2) what insight can we gain into how to approach treatment? To answer the first question, we can perhaps begin by examining where the plethora of data fits in the four-step schema (initiation, response, repair, adaptation) and generate a hierarchy of events with regard to causality and timing. This approach will provide a conceptual framework for evaluating data, thereby increasing our ability to synthesize multiple research findings into a coherent whole. The second question pertains to the translation of research findings into new therapeutic approaches. A critical step in a new approach would be to consider how clinical findings fit into our schema. A patient who is in the process of initial repair of the lesion would likely benefit from treatments that enhance the specificity and limit the scope of that repair. In contrast, a patient who is manifesting maladaptive physiology should receive treatments that modulate the adaptation. Thus, sulodexide may be effective in treating early, but not late, lesions in models of radiation-or diabetes-related nephropathy [50], while ACE inhibition does not prevent the development of microalbuminuria in type-1 diabetes [51] but is effective in blocking progression and, possibly, even reversing diabetic nephropathy [52]. This distinction among disease states is already applied by the oncologist, who utilizes morphological and molecular phenotyping to stage tumors and determine appropriate therapies. The result is a cocktail of drugs aimed at several different pathophysiological processes and tailored to the current state of the tumor. A similar concept would be of substantial benefit to pediatric kidney patients. Focusing treatment in this manner requires both an improved understanding of basic mechanisms and their regulation and the ability to determine, through biomarkers or other means, the stage at which a disease is manifested in a specific individual. Armed with such tools, we could approach therapy with a new sense of purpose and confidence.

Acknowledgments

Supported in part by grants R01-DK049362 and R01-DK075663 from the National Institute of Diabetes, Digestive and Kidney Diseases.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298:2038–2047. [PubMed: 17986697]
2. Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol*. 2008; 3:1563–1568. [PubMed: 18667744]
3. Thurau K, Boylan JW. Acute renal success. The unexpected logic of oliguria in acute renal failure. *Am J Med*. 1976; 61:308–315. [PubMed: 961698]
4. Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med*. 1999; 340:115–126. [PubMed: 9887164]
5. Bricker NS, Fine LG, Kaplan M, Epstein M, Bourgoignie JJ, Light A. “Magnification phenomenon” in chronic renal disease. *N Engl J Med*. 1978; 299:1287–1293. [PubMed: 714096]

6. Barnes JL, Hastings RR, De la Garza MA. Sequential expression of cellular fibronectin by platelets, macrophages, and mesangial cells in proliferative glomerulonephritis. *Am J Pathol.* 1994; 145:585–597. [PubMed: 8080041]
7. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet.* 1974; 2:556–560. [PubMed: 4140273]
8. Schnaper HW. The immune system in minimal change nephrotic syndrome. *Pediatr Nephrol.* 1989; 3:101–110. [PubMed: 2702078]
9. Sahali D, Pawlak A, Valanciute A, Grimbert P, Lang P, Remy P, Bensman A, Guellaen G. A novel approach to investigation of the pathogenesis of active minimal-change nephrotic syndrome using subtracted cDNA library screening. *J Am Soc Nephrol.* 2002; 13:1238–1247. [PubMed: 11961011]
10. Araya CE, Wasserfall CH, Brusko TM, Mu W, Segal MS, Johnson RJ, Garin EH. A case of unfulfilled expectations. Cytokines in idiopathic minimal lesion nephrotic syndrome. *Pediatr Nephrol.* 2006; 21:603–610. [PubMed: 16525836]
11. Lai KW, Wei CL, Tan LK, Tan PH, Chiang GS, Lee CG, Jordan SC, Yap HK. Overexpression of interleukin-13 induces minimal-change-like nephropathy in rats. *J Am Soc Nephrol.* 2007; 18:1476–1485. [PubMed: 17429054]
12. Heslan JM, Branellec AI, Pilatte Y, Lang P, Lagrue G. Differentiation between vascular permeability factor and IL-2 in lymphocyte supernatants from patients with minimal-change nephrotic syndrome. *Clin Exp Immunol.* 1991; 86:157–162. [PubMed: 1914229]
13. Garin EH, West L, Zheng W. Effect of interleukin-8 on glomerular sulfated compounds and albuminuria. *Pediatr Nephrol.* 1997; 11:274–279. [PubMed: 9203172]
14. Morales-Ruiz M, Fulton D, Sowa G, Languino LR, Fujio Y, Walsh K, Sessa WC. Vascular endothelial growth factor-stimulated actin reorganization and migration of endothelial cells is regulated via the serine/threonine kinase Akt. *Circ Res.* 2000; 86:892–896. [PubMed: 10785512]
15. Sung SH, Ziyadeh FN, Wang A, Pyagay PE, Kanwar YS, Chen S. Blockade of vascular endothelial growth factor signaling ameliorates diabetic albuminuria in mice. *J Am Soc Nephrol.* 2006; 17:3093–3104. [PubMed: 16988063]
16. Moller CC, Flesche J, Reiser J. Sensitizing the slit diaphragm with TRPC6 ion channels. *J Am Soc Nephrol.* 2009; 20:950–953. [PubMed: 18784209]
17. Barisoni L, Schnaper HW, Kopp JB. A proposed taxonomy for the podocytopathies: a reassessment of the primary nephrotic diseases. *Clin J Am Soc Nephrol.* 2007; 2:529–542. [PubMed: 17699461]
18. Barisoni L, Schnaper HW, Kopp JB. Advances in the biology and genetics of the podocytopathies: implications for diagnosis and therapy. *Arch Pathol Lab Med.* 2009; 133:201–216. [PubMed: 19195964]
19. Schiffer M, Bitzer M, Roberts IS, Kopp JB, ten Dijke P, Mundel P, Bottinger EP. Apoptosis in podocytes induced by TGF-beta and Smad7. *J Clin Invest.* 2001; 108:807–816. [PubMed: 11560950]
20. Schnaper HW, Hayashida T, Hubchak SC, Poncelet AC. TGF-beta signal transduction and mesangial cell fibrogenesis. *Am J Physiol Renal Physiol.* 2003; 284:F243–F252. [PubMed: 12529270]
21. Liu Y. Epithelial to mesenchymal transition in renal fibrogenesis: pathologic significance, molecular mechanism, and therapeutic intervention. *J Am Soc Nephrol.* 2004; 15:1–12. [PubMed: 14694152]
22. Shimizu A, Yamanaka N. Apoptosis and cell desquamation in repair process of ischemic tubular necrosis. *Virchows Arch B Cell Pathol Incl Mol Pathol.* 1993; 64:171–180. [PubMed: 8242176]
23. Sato M, Muragaki Y, Saika S, Roberts AB, Ooshima A. Targeted disruption of TGF-beta1/Smad3 signaling protects against renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction. *J Clin Invest.* 2003; 112:1486–1494. [PubMed: 14617750]
24. Schiffer M, Schiffer LE, Gupta A, Shaw AS, Roberts IS, Mundel P, Bottinger EP. Inhibitory Smads and TGF-beta signaling in glomerular cells. *J Am Soc Nephrol.* 2002; 13:2657–2666. [PubMed: 12397035]
25. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. *Am J Kidney Dis.* 2002; 39:1–11. [PubMed: 11774095]

26. Qi W, Twigg S, Chen X, Polhill TS, Poronnik P, Gilbert RE, Pollock CA. Integrated actions of transforming growth factor-beta1 and connective tissue growth factor in renal fibrosis. *Am J Physiol Renal Physiol*. 2005; 288:F800–F809. [PubMed: 15536170]
27. Bassuk JA, Pichler R, Rothmier JD, Pippen J, Gordon K, Meek RL, Bradshaw AD, Lombardi D, Strandjord TP, Reed M, Sage EH, Couser WG, Johnson R. Induction of TGF-beta1 by the matricellular protein SPARC in a rat model of glomerulonephritis. *Kidney Int*. 2000; 57:117–128. [PubMed: 10620193]
28. Goumenos DS, Tsakas S, El Nahas AM, Alexandri S, Oldroyd S, Kalliakmani P, Vlachoianis JG. Transforming growth factor-beta(1) in the kidney and urine of patients with glomerular disease and proteinuria. *Nephrol Dial Transplant*. 2002; 17:2145–2152. [PubMed: 12454225]
29. Guo G, Morrissey J, McCracken R, Tolley T, Liapis H, Klahr S. Contributions of angiotensin II and tumor necrosis factor-alpha to the development of renal fibrosis. *Am J Physiol Renal Physiol*. 2001; 280:F777–F785. [PubMed: 11292619]
30. Ophascharoensuk V, Giachelli CM, Gordon K, Hughes J, Pichler R, Brown P, Liaw L, Schmidt R, Shankland SJ, Alpers CE, Couser WG, Johnson RJ. Obstructive uropathy in the mouse: role of osteopontin in interstitial fibrosis and apoptosis. *Kidney Int*. 1999; 56:571–580. [PubMed: 10432396]
31. Ozawa Y, Kobori H, Suzuki Y, Navar LG. Sustained renal interstitial macrophage infiltration following chronic angiotensin II infusions. *Am J Physiol Renal Physiol*. 2007; 292:F330–F339. [PubMed: 16804106]
32. Floege J, Kriz W, Schulze M, Susani M, Kerjaschki D, Mooney A, Couser WG, Koch KM. Basic fibroblast growth factor augments podocyte injury and induces glomerulosclerosis in rats with experimental membranous nephropathy. *J Clin Invest*. 1995; 96:2809–2819. [PubMed: 8675651]
33. Terzi F, Burtin M, Hekmati M, Federici P, Grimber G, Briand P, Friedlander G. Targeted expression of a dominant-negative EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury. *J Clin Invest*. 2000; 106:225–234. [PubMed: 10903338]
34. Haseley LA, Hugo C, Reidy MA, Johnson RJ. Dissociation of mesangial cell migration and proliferation in experimental glomerulonephritis. *Kidney Int*. 1999; 56:964–972. [PubMed: 10469364]
35. Oikawa T, Freeman M, Lo W, Vaughan DE, Fogo A. Modulation of plasminogen activator inhibitor-1 in vivo: a new mechanism for the anti-fibrotic effect of renin-angiotensin inhibition. *Kidney Int*. 1997; 51:164–172. [PubMed: 8995730]
36. Wang A, Ziyadeh FN, Lee EY, Pyagay PE, Sung SH, Sheardown SA, Laping NJ, Chen S. Interference with TGF-beta signaling by Smad3-knockout in mice limits diabetic glomerulosclerosis without affecting albuminuria. *Am J Physiol Renal Physiol*. 2007; 293:F1657–F1665. [PubMed: 17804483]
37. Singh P, Deng A, Blantz RC, Thomson SC. Unexpected effect of angiotensin AT1 receptor blockade on tubuloglomerular feedback in early subtotal nephrectomy. *Am J Physiol Renal Physiol*. 2009; 296:F1158–F1165. [PubMed: 19211684]
38. Ichikawa I, Fogo A. Focal segmental glomerulosclerosis. *Pediatr Nephrol*. 1996; 10:374–391. [PubMed: 8792409]
39. Schlaich MP, Schmitt D, Ott C, Schmidt BM, Schmieder RE. Basal nitric oxide synthase activity is a major determinant of glomerular haemodynamics in humans. *J Hypertens*. 2008; 26:110–116. [PubMed: 18090547]
40. Ozeki M, Nagasu H, Satoh M, Namikoshi T, Haruna Y, Tomita N, Sasaki T, Kashihara N. Reactive oxygen species mediate compensatory glomerular hypertrophy in rat uninephrectomized kidney. *J Physiol Sci*. 2009; 59:397–404. [PubMed: 19593678]
41. Eberhardt W, Pfeilschifter J. Nitric oxide and vascular remodeling: spotlight on the kidney. *Kidney Int Suppl*. 2007; 106:S9–S16.
42. Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. *Kidney Int*. 2005; 67:404–419. [PubMed: 15673288]
43. Lovett DH, Johnson RJ, Marti HP, Martin J, Davies M, Couser WG. Structural characterization of the mesangial cell type IV collagenase and enhanced expression in a model of immune complex-mediated glomerulonephritis. *Am J Pathol*. 1992; 141:85–98. [PubMed: 1321565]

44. Oktem F, Sirin A, Bilge I, Emre S, Agachan B, Ispir T. ACE I/D gene polymorphism in primary FSGS and steroidsensitive nephrotic syndrome. *Pediatr Nephrol.* 2004; 19:384–389. [PubMed: 14986085]
45. Tesch GH. MCP-1/CCL2: a new diagnostic marker and therapeutic target for progressive renal injury in diabetic nephropathy. *Am J Physiol Renal Physiol.* 2008; 294:F697–F701. [PubMed: 18272603]
46. August P, Sharma V, Ding R, Schwartz JE, Suthanthiran M. Transforming growth factor beta and excess burden of renal disease. *Trans Am Clin Climatol Assoc.* 2009; 120:61–72. [PubMed: 19768163]
47. Schnaper, HW., Robson, AM., Kopp, JB. Nephrotic syndrome: minimal change nephropathy, focal segmental glomerulo-sclerosis and collapsing glomerulopathy. In: RW, Schrier, editor. *Diseases of the kidney and urinary tract.* 8th. Lippincott Williams & Wilkins; Philadelphia: 2006. p. 1585-1673.
48. Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, Oleksyk T, McKenzie LM, Kajiyama H, Ahuja TS, Berns JS, Briggs W, Cho ME, Dart RA, Kimmel PL, Korbet SM, Michel DM, Mokrzycki MH, Schelling JR, Simon E, Trachtman H, Vlahov D, Winkler CA. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet.* 2008; 40:1175–1184. [PubMed: 18794856]
49. Motoyoshi Y, Matsusaka T, Saito A, Pastan I, Willnow TE, Mizutani S, Ichikawa I. Megalin contributes to the early injury of proximal tubule cells during nonselective proteinuria. *Kidney Int.* 2008; 74:1262–1269. [PubMed: 18769366]
50. Rossini M, Naito T, Yang H, Freeman M, Donnert E, Ma LJ, Dunn SR, Sharma K, Fogo AB. Sulodexide ameliorates early but not late kidney disease in models of radiation nephropathy and diabetic nephropathy. *Nephrol Dial Transplant.* 2010; doi: 10.1093/ndt/gfp724
51. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, Drummond K, Donnelly S, Goodyer P, Gubler MC, Klein R. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med.* 2009; 361:40–51. [PubMed: 19571282]
52. 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. [PubMed: 9654536]

Fig. 1.
Theoretical schema for the pathogenesis of chronic kidney disease. *ECM* Extracellular matrix. See text for details

Fig. 2.

Steps in the development of chronic kidney disease (CKD) secondary to idiopathic focal segmental glomerulosclerosis (FSGS). An initial wave of cytokines, representing the injury (genetic and/or environmental) and response stages of disease pathogenesis, leads to proteinuria. Different mechanisms affecting cytoskeletal/slit diaphragm integrity may mediate proteinuria. For those that cause sufficient injury, a repair process is initiated, with a second wave of cytokine expression. If this repair is not physiologically controlled, a maladaptive state leads to a chronic cycle of injury and misdirected repair, leading to death and structural loss in the process of scar formation. In contrast, minimal change disease (MCD) involves only the left-hand part of the diagram, from cytokines to proteinuria.

SNGFR Single nephron glomerular filtration rate

Clinical Status	Pathogenetic Stage	Clinical Disease Phase	Contributing Factors
Genetic Predisposition	Injury	Initiation	Infection Inflammation Environmental stimulus
Initial Lesion	Response		
Resistant FSGS	Repair	Consolidation	Low nephron number Hypertension Glomerular overload
Progression to CKD	Maladaptation	Progression	Nephron loss "Progression" genes Excessive mediator response

Fig. 3.

Stages of progressive kidney disease. Using idiopathic FSGS as an example, temporal/functional relationships are shown among clinical status, pathogenetic stage according to the conceptual construct proposed in this essay, the phase of the clinical disease, and some of the factors that contribute to progression in the different stages of the disease. *Resistant FSGS* refers to the stage at which the disease is relatively resistant to standard forms of therapy for glomerular disease. Please note that a similar table could be prepared, for example, to describe the status of a patient who has nephron loss from polycystic kidney disease