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Progression of Glomerular and Tubular Disease

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Abstract

Chronic kidney disease may be stimulated by many different etiologies, but its progression involves a common, yet complex, series of events that lead to the replacement of normal tissue with scar. These events include altered physiology within the kidney leading to abnormal hemodynamics, chronic hypoxia, inflammation, cellular dysfunction and activation of fibrogenic biochemical pathways. The end result is the replacement of normal structures with extracellular matrix. Treatments are presently focused on delaying or preventing such progression, and are largely nonspecific. In pediatrics, such therapy is further complicated by both pathophysiological issues that render children a unique population.

Progression of glomerular and tubular disease is clinically defined by a persistent decline in glomerular filtration rate (GFR) that results in chronic kidney disease (CKD) and may lead to end-stage kidney disease (ESKD). Clinical assessment of the velocity of GFR deterioration can be a challenging task in children, since not only is GFR a function of age, gender, and method of its measurement [1], but also the decline may take several years, and thus be difficult to assess. This has practical implications for patient care and research. Several methods/formulas for GFR determination and surrogate markers of kidney disease progression have been developed and validated to alleviate this problem [2]. Morphologically, it has been long noted that impairment of GFR correlates better with the extent of tubulointerstitial injury rather than glomerular injury [3]. However, the reciprocal interaction of primary glomerular and tubular injury makes difficult, and perhaps renders moot, the question of the primacy of the glomerular vs the tubulointerstitial lesion.

Diseases Causing Progression in Children

Progression of glomerular and tubular disease depends on several host factors (i.e. age, sex, race, prenatal course, hypertension, genotype, environmental exposure) and the nature of the underlying kidney disease. The most common causes of CKD in children involve congenital renal and urologic anomalies. Other diseases commonly underlying CKD in children include focal segmental glomerulosclerosis (FSGS), hemolytic uremic syndrome (HUS), immune

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complex diseases, and hereditary nephropathies, such as Alport's disease [4]. The incidence of CKD in children has been stable in the last decade, in contrast to the adult population where the incidence is sharply increasing. It should be noted that the increase in adults may be attributed to the rising prevalence of diabetes and hypertension. Although the resulting CKD occurs primarily in adulthood, it is worth remarking that the underlying causes of diabetes and hypertension likely have their origins in childhood [6].

PATHOPHYSIOLOGY OF CKD

Various animal models of glomerulosclerosis show that nephron loss starts with glomerular extracapillary lesions, and that podocyte injury or dysfunction plays a central role (REFWiggins, KI 2007 review) Kriz and colleagues have proposed that the initial events leading to extracapillary lesions include the formation of adhesions between glomerular capillary loops and Bowman's capsule as a consequence of denudation of the GBM [7], and subsequent activation of mesangial and endothelial cells. The result is decreased renal glomerular filtration surface area and the accumulation of extracellular matrix (ECM) in a segmental pattern (sclerosis) that suggests mesangial involvement [11]. This *misdirected filtration* hypothesis is in contrast to another hypothesis, one based upon the concept of *podocyte depletion*, where an absolute number of podocytes is proposed to be present in a particular glomerulus. When these are injured or detached, the remaining podocytes migrate and undergo hypertrophy in order to cover the external aspect of all capillary loops. When the area requiring such “coverage” exceeds the capacity of the remaining podocytes, the resulting hypertrophy and dysfunction causes glomerulosclerosis. It should be recognized that these two hypotheses are not mutually exclusive. For example, a capillary loop denuded because of podocyte failure is more likely to adhere to Bowman's capsule.

Several other morphologic features of CKD are characteristic and affect the entire nephron: loss of normal renal cells, primarily through apoptosis, and infiltration by monocytes and/or macrophages into the tubulointerstitium, with subsequent fibrosis [11]. Review of experimental and clinical studies suggests common mechanisms that contribute to this pathologic process. These include abnormal glomerular hemodynamics, hypoxia, genetic factors, effects of proteinuria, hypertension, and the abnormal production of cytokines and growth factors. Each of these processes represents an abnormal adaptation to the primary injury, resulting in molecular and cellular disarrangement and, ultimately, renal dysmorphology.

In particular, *excessive nephron load* has been implicated in progressive disease. Increased glomerular hemodynamic stress result from increased glomerular circulation, hydrostatic pressure or filtered load, either from altered autoregulation or in response to the loss of other nephrons. Increased filtered load of proteins taxes the reabsorptive capacity of the renal tubules, particularly the proximal tubules [12]. Reabsorption of biologically active proteins may activate cells in the tubulointerstitium or recruit inflammatory cells from elsewhere. The result is changes in cell phenotype and function that will be discussed later in this review.

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Renal scarring results from increased synthesis and decreased breakdown of extracellular matrix (ECM). The abnormal ECM contains an excess of normal components such as fibronectin, laminin, proteoglycans, and type IV collagen [14], as well as matrices not usually found such as type I collagen in the glomerulus. These molecular changes in the ECM composition alter the ways the cells interact with the ECM, which in turn affects gene regulation and expression in response to specific growth factors.

MECHANISMS OF PROGRESSION

Physiological factors in progression

It is known that hypertension is associated with progression, or at least accelerated progression [15]. Increased hydrostatic pressure at the level of both the single nephron and the whole kidney has been implicated. However, Yoshida and colleagues reported an elegant series of studies in which hyperfiltration, rather than hypertension, appeared to be the significant factor [16]. Hypertension also may be a significant cause of tubulointerstitial fibrosis, as indicated by studies in hypertensive rats where one kidney was protected from elevated perfusion pressure [17]. Opinion is divided regarding whether the critical factor is high pressure or whether the hypertension reflects excess renin activity. A large number of studies in humans and in animal models have indicated that renin antagonists, angiotensin-receptor blockade (ARB) or angiotensin converting enzyme (ACE) inhibition slows the progression of renal failure [18]. In some, but not all, studies comparing renin-angiotensin system (RAS) antagonists with calcium channel blockers, it was found that the therapies were equally effective. It is likely that the underlying cause of hypertension or of kidney disease was an important determinant of outcome. RAS antagonists also may have additional beneficial effects on proteinuria or on the excess production of additional mediators that promote real disease progression [19].

New data suggest that specific cellular interactions with the surrounding extracellular matrix (ECM) are important in progression, since integrin-deficient mice may manifest progressive renal disease [20]. The role of integrins in fibrogenic signaling [21,22] suggests that cell-matrix interactions may be one way in which the physiological effects of local hypertension have an impact on ECM accumulation. Few relevant studies comparing calcium channel blockers with ACE/ARB have been performed solely in children.

Chronic hypoxia is associated with the loss of peritubular capillaries and the development of interstitial fibrosis that further impairs oxygen diffusion and supply to tubular and interstitial cells, resulting in a vicious cycle [23]. Peritubular capillaries undergo spasm and, eventually apoptosis, during the course of CKD [24]. The hypoxia-inducible transcription factor, HIF-1α, is expressed in high quantities in many cases of progressive renal disease [25] and may play a role in the production of cytokines or of signaling molecules that mediate progression. Recent observations regarding the role of asymmetric dimethyl arginine (ADMA) in the cardiovascular complications of CKD [26] also may have implications for the local circulation in the kidney. Alternatively, tubular loss could be the primary event, with subsequent capillary dropout. Chevalier and Forbes cite data indicating that the immediately post-glomerular proximal tubule is particularly sensitive to ischemia

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and reactive oxygen species, and its irreversible damage could lead to the generation of atubular glomeruli, with consequent loss of function [27].

Genetic factors—Gene polymorphisms in the RAAS system, including ACE, angiotensinogen and the angiotensin type 1 receptor, have been associated with diabetic nephropathy, IgA nephropathy and uropathies [28] [31] [32] [33]. The ACE DD genotype is associated with increased RAS activity, and was shown to be increased in patients with IgA nephropathy who experienced progressive decline in renal function during follow-up compared with those whose renal function remained stable over the same time period [33]. Polymorphisms of TGF-β have been implicated in hypertension and progressive fibrosis. The Arg 25 polymorphism is increased in African Americans [34].

Additional genetic factors for which specific gene mutations or polymorphisms have not been identified are suggested by the observation that certain ethnic backgrounds or familial patterns may contribute to progression. In the Pima Indians, a population with extremely high incidence of type 2 diabetes mellitus [35], some families experience a very high occurrence of ESRD, whereas others do not. Patients of African American descent experience a higher frequency and rate of progression than do Caucasians with similar disease [36], suggesting a predisposition that has been attributed to increased hypertension [37], increased glomerular size [38], greater levels of circulating TGF-β [34], or additional, unknown factors. Low nephron number has been associated with increased incidence of hypertension [39] and kidney disease [40]; these studies suggest the hypothesis that low nephron number contributes to hyperfiltration and/or nephron hypertrophy. However, it is likely that an additional factor is involved, since the presence of a congenitally solitary kidney or loss of a kidney from injury, or due to organ donation is not commonly associated with CKD [41].

Male gender is associated with a more rapid progression of kidney disease in several animal models of renal injury and in human kidney disease, independent of other risk factors such as systemic blood pressure or serum lipid levels [43]. Experimental data suggest that the impact of gender on renal disease progression may be due to genetically determined differences between the sexes in renal structure and function as well as to receptor-mediated effects of sex hormones.

Environmental exposures

One of the best-documented environmental exposures associated with progression of renal disease is exposure to lead. Large-scale epidemiologic studies have noted associations between environmental exposure to lead, even at low levels, and CKD [45]. Although lead exposure amongst children in U.S. has declined in recent years, the situation is different in developing countries [46], and there is well established longitudinal relationship between lead exposure in early childhood and bone lead levels in adulthood [47].

Exposure to high phosphorus intake that results in high calcium–phosphorus product in patients with established CKD leads to vascular and tubulointerstitial calcifications, which in turn stimulate tubulointerstitial inflammation and fibrosis and lead to progression of renal and cardiovascular disease [48].

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Cellular determinants of progression

The podocyte in progressive renal disease—The discovery of nephrin as the gene that is mutated in Finnish-type congenital nephrotic syndrome [49] has led to a major shift in our understanding of how the glomerular filter works and of the role of podocyte injury in chronic, progressive kidney disease. Nephrin is a podocyte-specific protein, and subsequently, mutations of other, podocyte-specific proteins also have been associated with glomerulosclerosis (Table 1). Functionally, the development of progression and glomerulosclerosis (GS) in several human and experimental diseases is associated with podocyte loss and podocytopenia [50] [51] [52]. There is significant correlation between the development of extracapillary lesions on renal histology and urinary podocyte number [55]. Causes of podocytopenia include apoptosis, detachment from the GBM, and the inability or lack of podocytes to proliferate [56]. In turn the remaining podocytes may fail to cover completely the glomerular basement membrane (GBM) and thus parietal epithelial cells of Bowman's capsule may gain access to bare areas of the GBM, forming adhesions and leading to segmental glomerulosclerosis [56] [57] [58].

Apoptotic podocytes are excreted in the urine [55, 62]. Several reports describe the presence of live podocytes in the urine in glomerular diseases [63, 64]. Quantitative determination of podocyte number in human urine was found to be a useful diagnostic tool for differentiating glomerular from nonglomerular diseases, or inflammatory from noninflammatory diseases, and as a marker of disease progression [55, 64-66]. Pagtalunan et al. [50] showed that subjects type II diabetes who had more advanced proteinuria and glomerular matrix accumulation also had fewer glomerular podocytes than those who had diabetes for the same length of time but did not have proteinuria or glomerulosclerosis. In contrast, other glomerular cells did not decrease in number in the same glomeruli [50]. Pima Indians with a lesser podocyte number developed macroalbuminuria faster than those who had a greater podocyte number [65]. Lemeley et al. [52] showed that podocyte loss in IgA nephropathy (IgAN) is associated with increasing disease severity. In that study, the degree of podocytopenia was related to the degree of glomerular sclerosis, impairment of permselectivity, and GFR. In contrast, the authors did not find corresponding correlations between these indices of injury and the number of mesangial and endothelial cells [52]. Podocyte inability to proliferate prevents the restoration of a normal podocyte number [67]. This is in contrast with mesangial and endothelial cells, which readily proliferate in response to many forms of injury [68]. Tubular cell numbers are affected in polycystic kidney disease, where the precisely controlled balance between cellular proliferation and apoptosis is disturbed with increased proliferation in both non-cystic and cystic tubules [70]. Kidneys from patients with ADPKD have high levels of both apoptosis and cellular proliferation [72].

Mesangial cells—As mentioned above, mesangial cells may proliferate, and increased mesangial cell number in glomerulosclerosis is associated with a poor response to therapy [73]. Given the mesangial pattern of ECM expression seen with many forms of progressive glomerular disease, it is likely that the mesangial cell is a significant contributor to the scarring pattern that is observed.

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Endothelial cells—The endothelial cells deliver oxygen and nutrients and are essential to the survival of other cells [74]. Endothelial proliferation and peritubular capillary growth has been observed in progression models that are based on reduction of nephron mass [75]. Conversely, endothelial cells play a role in the repair of capillaries and microaneurysms in the Thy-1 model of glomerulonephritis [76]. While early production of vascular endothelial cell growth factor (VEGF) may play a role in acute disease pathogenesis, under more chronic conditions VEGF may promote healing [77]. Ostendorf et al. [78] showed that inhibition of VEGF leads to impairment of capillary repair and results in progressive renal damage, and Masuda et al. [79] have shown that VEGF administration enhances capillary repair and improves renal function in Thy-1 model of glomerulonephritis. However, increased angiogenesis and VEGF expression leads to increasing vascular permeability and promotes cyst formation in the cysts of ADPKD [80].

Inflammation—Macrophage colony stimulating factor secreted by tubular cells during renal injury induces local macrophage proliferation and infiltration in the kidney [81]. These cells in turn produce more cytokines that amplify cell proliferation and infiltration. In addition macrophage-derived cytokines, including interleukin IL-1, IL-6, and TNF-α, inhibit expression of vascular endothelial growth factor (VEGF), impairing angiogenesis and promoting capillary loss [82]. Macrophage infiltration in the interstitium correlates with the degree of renal dysfunction [84]. This vicious cycle promotes cell apoptosis and fibrosis [86] [81]. However, macrophages also may play a beneficial role in scarring. In studies of bone marrow transplantation in wild-type mice and mice with unilateral ureteral obstruction reconstituted with either wild type macrophages or macrophages devoid of the AT1a receptor, severe interstitial fibrosis was observed in mice with AT1a deficient macrophages, even though they had fewer infiltrating macrophages. This result suggests that the macrophage AT1a receptor plays a protective role in fibrogenesis [87].

Interstitial mast cells have been associated with severity of interstitial fibrosis in patients with various glomerulonephritides [88]. There is also an association of stem cell factor produced by mast cells and myofibroblasts that suggests, these cells may be involved in progression of interstitial fibrosis as well [88]. Dendritic cells have been identified in the tubulointerstitium and could play a role in antigen presentation and immune activation of the kidney [89].

Epithelial-to-mesenchymal transition (EMT) as a factor in progression—A critical issue in the cellular response is the phenotype of the cell. Epithelial cells are unlikely to produce non-basement membrane ECM when epithelioid in nature, but when they dedifferentiate they produce a more primordial mesenchyme. Thus, the mesangial cell usually produces type IV collagen, but when injured may produce more type I collagen. There is significant disagreement regarding the origin of ECM-producing cells in the renal scar. Sources of fibroblasts include EMT of renal tubular cells or podocytes [63] [90], activation of resident interstitial stem cells that differentiate into myofibroblasts [92], fibroblasts that migrate into tissue from adjacent areas [93], or macrophages that are recruited to the lesion and undergo transition to myofibroblasts. The resulting phenotype, which has features of both smooth muscle cells and fibroblasts, have been reported to play a

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role in the fibrogenic process in both glomeruli and tubules, producing and secreting α2(I) and α2(III) collagens and fibronectin.

Biochemical pathways regulating ECM accumulation

An important determinant of scarring in the kidney is the balance between ECM synthesis and degradation [94]. In addition to the synthesis of ECM, the net abundance of matrix proteins is controlled by two degradative pathways. In one, the matrix metalloproteinase (MMP) pathway, a large number of enzymes with varying specificity for different ECMs facilitate the degradation of matrix [95]. These are opposed by the tissue inhibitors of metalloproteinases (TIMPs) [96]. A second pathway involves the tissue- and urokinase-type plasminogen activators (tPA and uPA, respectively) [97], which are opposed by the plasminogen activator inhibitors, PAI-1 and PAI-2. Many of these molecules have shown increased expression or activation in kidney disease, particularly TIMP-1 [98] and PAI-1 [99] and mice genetically altered to be deficient in PAI-1 do not respond to fibrogenic stimuli with nearly the degree of scarring shown by wild-type mice [100].

Molecular regulation of progression

A number of cytokines have been implicated in progression. Prominent among them is transforming growth factor (TGF)-β, a pleiotropic molecule that stimulates many of the events involved in progression, including EMT, apoptosis, ECM synthesis, generation of reactive oxygen species (ROS) and PAI-1 production [101]. Cytokine mediators that stimulate proliferative changes include basic fibroblast growth factor (FGF-2) [102] and platelet-derived growth factor (PDGF) [103]. Endothelin-1 mediates vasoconstriction and also stimulates the production of aldosterone, recently implicated in fibrogenesis as well [104]. Connective tissue growth factor (CTGF), a downstream mediator of TGF-β that stimulates the synthesis of several ECM proteins, has been associated with progression of several forms of renal injury [105].

In the cells of the kidney, several signal transduction pathways have been identified that appear to play a prominent role in progression. The TGF-β pathway is mediated by the Smad family of signal transduction proteins [106]. Several other pathways have been identified as being engaged in cross-talk with Smads, including ERK MAP kinase [107], p38 MAP kinase [108], phosphatidylinositol-3-kinase (PI3K) [109], protein kinase C (PKCδ) [110], PKCβ and Rho A. Rho A has been implicated in EMT [111] and diabetic nephropathy [112]. PI3K [113] and PKCβ [114] have been implicated in diabetic nephropathy.

Overview of mechanisms of progression

Figure 1 shows an overall schema of mechanisms of progression mentioned in this review. All of the parameters described may interact. For example, genetic factors may influence the development of hypertension, or genes may be activated by environmental factors. Once these factors have been activated, a variety of cellular and biochemical pathways mediate cellular dedifferentiation and ECM accumulation.

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APPROACHES TO TREATMENT

Specific treatment

Progressive kidney disease is multifactorial in nature. Its specific treatment depends upon the underlying etiology. Thus, type 1 diabetic nephropathy is best treated by regulation of glucose metabolism, whereas type 2 diabetic nephropathy may best be treated by a combination of treatments directed at glucose control, vascular reactivity and, where appropriate, weight reduction. CKD secondary to inflammatory disease is best directed at the most appropriate treatment for the underlying cause. In FSGS, therapy largely involves calcineurin antagonists such as cyclosporine or tacrolimus [115] [116]. Additional therapies include glucocorticoids, cytotoxic agents or mycophenolate mofetil [118]. The calcineurin antagonists have proven most effective of these choices, although none of these treatments is fully effective. In part, this may be because FSGS itself is a multifactorial disease. In those cases where the primary cause is a genetic deficiency of a podocyte protein, even these "specific" treatments do not address the primary problem in disease pathogenesis.

Nonspecific treatment

Treatment of proteinuria—In most studies, proteinuria is associated with progression of chronic kidney disease. Although there remains some question regarding whether proteinuria is a marker of disease [119, 120] or a cause, it is clear that the association is a strong one, and that cases in which treatments significantly reduce proteinuria are more likely to show delay or prevention of progression in children and adults [121, 122]. Therefore, ACE inhibition and/or angiotensin receptor blockade is now recommended as adjunct therapy [123] in most cases of CKD.

Treatment of hypertension—Hypertension is associated with accelerated progression to ESKD in children [15]. For this reason, tight BP control is an essential adjunct treatment. Most recent guidelines by the Joint National Committee in the US define 120/80 mmHg as the upper limit of the 'optimal' blood pressure range, particularly when proteinuria is present [123]. These blood pressure targets are equivalent to the 50th to 75th distribution percentile in the general young adult population. In adults blood pressure > 130/80 should be actively lowered by therapeutic intervention in CKD patients [124]. Although it is as yet unknown whether these blood pressure targets hold true for pediatric population and whether glomerular damage in children correlates with absolute or age-specific relative blood pressure, K/DOQI guidelines on blood pressure control in CKD children adopted the recommendations of the task force that target blood pressure should be <90th percentile for normal values adjusted for age, gender, and height percentile [125]. In addition to the absolute blood pressure level normal diurnal blood pressure pattern may play a significant role in renal failure progression, as "nondipping" is an independent cardiovascular risk factor associated with more rapid progression of renal failure in adult CKD patients [126]. ACE inhibition and/or angiotensin receptor blockade is an effective and safe antihypertensive and antiproteinuric approach in children with CKD-associated hypertension [127] [128].

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Treatment of calcium-phosphate metabolism—Hyperphosphatemia, hyperparathyroidism, lack of active vitamin D, and excess of the phosphaturic hormone FGF 23 lead to disturbances in calcium-phosphate metabolism and play a role in CKD progression [129]. Dietary phosphate restriction in adult patients with CKD is associated with stabilization of kidney function [130]. This however, has not been demonstrated in large scale pediatric studies [131]. Calcium-free phosphate binders may prove beneficial beyond phosphate lowering due to their pleiotropic effects, i.e. lipid-lowering and anti-inflammatory properties [132]. High and prolonged level of PTH exposure is toxic to many organs, including the heart, bones, skeletal muscle, nerves, and reproductive system [133]. Early control of PTH production by parathyroid glands with phosphate restriction and administration of vitamin D is crucial because sustained hyperactivity of parathyroid glands leads to nodular hyperplasia that largely irreversible and resistant to vitamin D and calcium regulation [134]. Treatment with nonhypercalcemic doses of active vitamin D and its analogues attenuates renal failure progression in non-inflammatory and inflammatory models of CKD. Active vitamin D has negative endocrine regulation of the RAS, anti-inflammatory, antifibrotic and antiproteinuric properties [135] [136] [137]. Recently FGF23 has been shown to be an independent predictor of progression of renal disease in adult patients with nondiabetic CKD [138].

Treatment of anemia—Treating anemia early in renal failure patients significantly slows the decline of renal function and delays the need for renal replacement therapy [139]. In animal models of kidney injury the mechanism of renoprotection of recombinant human erythropoietin (EPO) appears to be mainly mediated by a reduction of apoptotic cell death [140] and maintenance of the podocyte actin cytoskeleton and nephrin expression [141]. No conclusive studies have indicated a benefit of EPO in slowing pediatric CKD progression.

Other adjunct treatments—Lipid-lowering therapy reduces cardiovascular morbidity and mortality in adults with CKD although this effect has not been shown in patients with ESRD [142]. Statins may have renoprotective properties not only by their lipid-lowering but also by lipid-independent pleiotropic effects. Statins reduce oxidative stress and improve endothelial function [143]. There is evidence for synergistic effects of statins and RAS inhibitors on retardation of renal disease progression [144]. However, the renoprotective effects of statins, although significant, are quantitatively small [145]. There are no studies demonstrating the usefulness of statins in children with CKD.

Antioxidants such as probucol [146] or Vitamin E [147] have been suggested as treatments for some forms of progressive kidney disease, including that associated with IgA nephropathy. The efficacy of these treatments remains unproven. No conclusive studies have indicated a benefit of plasmapheresis.

Potential new approaches to therapy

New treatments that have been suggested include those directed at some of the signal transduction mechanisms mentioned earlier in this review. These include PI3K antagonists [148]; PKCβ antagonists [149]; and fasudil, a Rho A inhibitor [150]. Other experimental

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anti-fibrotic agents include sulodexide [151], and PPAR antagonists [152]. Smad7, an inhibitory Smad, may also have therapeutic potential [153].

Pediatric-specific considerations

Although The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines were initiated in 1997 by the National Kidney Foundation, the large majority of the pediatric guidelines are still opinion based because of the lack of evidence-based data [131] [124]. Outcome measures used in adults i.e. mortality, cardiovascular complications, have only limited validity in pediatric studies. Some K/DOQI guideline goals may not be applicable i.e. cholesterol, and many drugs have not been tested for efficacy and safety in children [154].

Another unique consideration of the pediatric patient with CKD progression includes emphasis on the importance of growth and development. *Growth failure* has long been recognized in children with chronic renal failure [155]. Abnormalities in GH and IGF-I signal transduction and the interaction of these pathways with ghrelin, myostatin, and the suppressor of cytokine signaling (SOCS) family are responsible for many important complications seen in chronic kidney disease (CKD), such as growth retardation and cachectic wasting, as well as disease progression [156]. Growth retardation in CKD is associated with increased morbidity and mortality [157]. Treatment with recombinant human growth hormone in CKD is safe, efficacious and widely accepted [158]. Newer treatment modalities targeting the GH resistance with recombinant human IGF-1 (rhIGF-1), recombinant human IGFBP3 (rhIGFBP3) and IGFBP displacers are under investigation and may prove to be more effective in treating growth failure in CKD [160] [161].

Regression

Finally, all of the treatments described here are aimed at preventing the progression of disease. Recent studies by several investigators have suggested that it may be possible to reverse the renal lesion by promoting the formation of new nephrons or capillary structures [122] [162]. Possible approaches include pro-angiogenic therapy, regulating the dedifferentiation and redifferentiation of cells to promote the formation of new structures [163], or the use of stem cell treatments [164]. While the challenges inherent to these approaches are daunting, the potential rewards of success mandate continued studies toward implementation.

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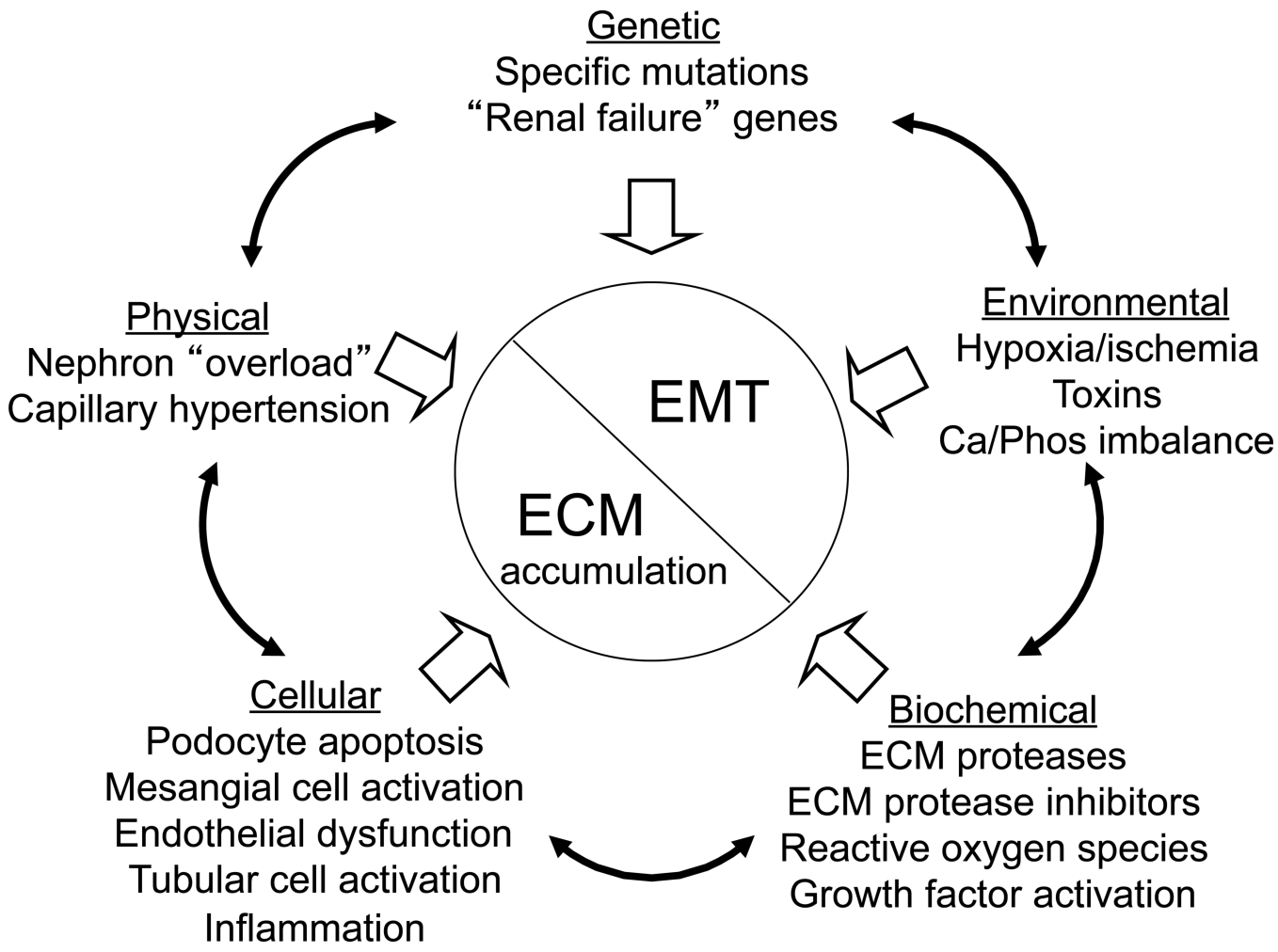

Figure 1.
Factors underlying or influencing progression of kidney disease.

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Table 1

Podocyte proteins for which mutations have been related to FSGS or its variants*

Protein	Gene	Function
Podocyte-specific		
α-actinin-4	ACTN4	Cytoskeletal assembly
CD2-associated protein	CD2AP	Slit diaphragm complex
Nephrin	NPHS1	Cell-cell interaction
Podocin	NPHS2	Cell-cell interaction
Transient receptor potential ion channel 6	TRPC6	Channel protein
Not podocyte-specific		
Lmx1b	Lmx1b	Transcription factor
Laminin β2	LAMB2	ECM protein
Wilms tumor-1	WT1	Transcription factor

* Data taken from reference [118].