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Review

The fate of nephrons in congenital and heritable renal disorders

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Learned lessons, changing practice and cutting-edge research

Abstract

Most chronic kidney disease in infants and children results from congenital anomalies of the kidneys and urinary tract, including obstructive nephropathy. Although less common, inherited disorders such as polycystic kidney disease (PKD) and cystinosis also lead to progressive tubular injury and nephron loss. At the present time, therapies to slow progression of kidney disease are mainly directed renal interstitial fibrosis, a final common pathway. To target earlier events in congenital renal disorders, we have investigated in animal models the response of the renal proximal tubule, which appears to be particularly susceptible to injury. Unilateral ureteral obstruction (UUO) causes marked oxidative stress and rapid death of proximal tubular cells in the adult mouse, leading to the formation of atubular glomeruli. This occurs also following UUO in the neonate (during completion of nephrogenesis), but tubular cell death is delayed until proximal tubular mitochondrial maturation is complete. In the *pcy* mutant mouse, a model of autosomal dominant PKD, tubular cysts develop in the neonatal period, and progressively enlarge, eventually causing obstruction of neighboring nephrons and formation of atubular glomeruli. In the *ctns* mutant mouse with nephropathic cystinosis, injury results from accumulation of cystine crystals. This results in oxidative stress and stimulates flattening (rather than death) of proximal tubular cells ("swan neck deformity"), and onset of the Fanconi syndrome. Progression to severe proximal tubular atrophy and formation of atubular glomeruli develops in later adult life. These studies suggest that early treatment of congenital renal disorders should target protection of proximal tubules from oxidative injury. We are currently investigating the use of antioxidants that are selectively concentrated in mitochondria. Since children with congenital renal disorders are born with a reduced nephron number (which cannot be regenerated), every effort must be made to preserve remaining nephrons throughout adult life.

Keywords

Kidney development, obstructive nephropathy, polycystic kidney disease, cystinosis, chronic kidney disease, antioxidants.

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Introduction

Over 50% of chronic kidney disease in children results from congenital anomalies of the kidneys and urinary tract (CAKUT), and obstructive nephropathy is the leading cause [1]. Although developing during nephrogenesis (in fetal life), the molecular basis for most of these disorders remains unknown, and few follow a Mendelian inheritance pattern. In contrast, polycystic kidney disease (PKD) and related ciliopathies are inherited as autosomal dominant or recessive diseases, and develop either in fetal or postnatal life [2]. Although the rate of progression of this group of disorders is largely dependent on the particular mutation, some patients develop significant cystic changes in fetal life, whereas others do not deteriorate until adulthood. Cystinosis is a rare autosomal recessive disorder due to mutation in *cystinosin*, a cystine transporter [3]. Affected infants accumulate cystine primarily in renal proximal tubules, leading to Fanconi syndrome, impaired somatic growth, and kidney failure in the second decade [3].

Nephrogenesis is complete in fetal life, and following birth, growth of proximal tubules is responsible for over 50% of the increase in renal mass during postnatal growth [4]. With transition from placental to extrauterine life, glomerular filtration rate increases rapidly, demanding increased tubular reabsorption fueled by proximal tubular mitochondria, which switch from glycolytic to oxidative metabolism [5]. As with CAKUT and inherited renal disorders, intrauterine growth restriction or preterm birth also lead to reduced nephron number in the neonate, which results in renal hyperfiltration and accelerated nephron loss [6]. Because this process eventually leads to glomerulosclerosis and interstitial fibrosis, intrarenal deposition of collagen has become a primary therapeutic target [7]. Using mouse models of congenital and heritable renal disease, we have developed a new paradigm for progression of chronic kidney disease. Our studies suggest proximal tubular injury as a primary target of chronic kidney disease, rather than on interstitial fibrosis, which is more likely a consequence than a cause of renal failure.

Congenital obstructive nephropathy

In the adult mouse, 7-14 days of unilateral ureteral obstruction (UUO) leads to the loss of over 50% of proximal tubular mass as a result of cell death, but less than a 5% increase in fractional interstitial collagen deposition [8]. In the adult mouse, 14 days of UUO results in loss of 85% of normal nephrons, which become atrophic with formation of "atubular" glomeruli as a result of proximal tubular cell death [9]. Healthy proximal tubular cells are packed with mitochondria, whose metabolism results in the formation of superoxide localized to the basal surface of the cells. Chronic UUO results in proximal tubular oxidative stress, which leads to loss of mitochondria within 7-14 days [8]. Nephrogenesis in the mouse is not complete until the third day of life, and UUO in the neonatal mouse delays nephron maturation. In contrast to rapid proximal tubular cell death in the adult, following UUO in the neonate widespread cell death is delayed until after 14 days of age, concurrent with proximal tubular maturation [10]. Unlike the human glomerulus, in which flattened parietal epithelial cells line all of Bowman's capsule, columnar epithelial cells indistinguishable from contiguous proximal tubular cells extend around the urinary pole of Bowman's capsule as nephrons mature. These cells bind *Lotus tetragonolobus* lectin, such that *Lotus*-staining glomeruli serve as an index of nephrons with mature, intact glomerulotubular junctions. In contrast to the adult, UUO in the neonate leaves mitochondria intact until 21-28 days, at which time mitochondria are lost [10]. Early "protection" of proximal tubules following UUO in the neonate likely results from persistence of glycolytic metabolism after birth, with gradual transition to oxidative metabolism during postnatal maturation. These studies suggest that progressive proximal tubular injury in congenital obstructive nephropathy is accelerated after birth, and that delay in surgical intervention in the face of significant obstruction may result in long-term loss of potential recovery.

Polycystic kidney disease (PKD)

PKD in the infant is most often inherited as an autosomal recessive disorder, but autosomal dominant PKD ("adult-type") can also present in the neonate [2]. Mouse models of PKD include the early-onset *cpk* mutant (a model of autosomal recessive PKD), and the late-onset *pcy* mutant (a model of autosomal dominant PKD) [11]. The *pcy* mouse develops multiple cysts in the neonatal period, with progressive enlargement of the cysts over the first 6 months of life. This is associated with obstruction of adjacent nephrons, with progressive proximal tubular atrophy and cell death, leading to the formation of atubular glomeruli [12]. These results suggest that therapies directed at reduction in cyst expansion may protect unaffected nephrons from obstructive injury, thereby delaying progression to renal failure.

Nephropathic cystinosis

Cystinosis is a rare autosomal recessive disorder resulting in progressive accumulation of cystine in proximal tubular cells [3]. This results in proximal tubular oxidative injury and mitochondrial dysfunction, but nephrons do not respond initially by massive proximal tubular cell death. Instead, proximal tubular cells undergo phenotypic transition from columnar to flattened cells with thickened tubular basement membranes [13]. This begins at the glomerulotubular junction and progresses distally down the tubule, resulting in the characteristic "swan neck" deformity. This response maintains patency of the nephrons, but loss of mitochondria and of transporters leads to reduced reabsorption of components of the glomerular filtrate and to the Fanconi syndrome. There is progression of proximal tubular maturation during the first 6 months of life, followed by progressive decreasing proximal tubular mass, and eventually by the formation of atubular glomeruli [13].

Congenital kidney disease interferes with renal development and causes postnatal renal injury

As shown in **Fig. 1**, CAKUT or inherited renal disease can result in renal hypoplasia or dysplasia,

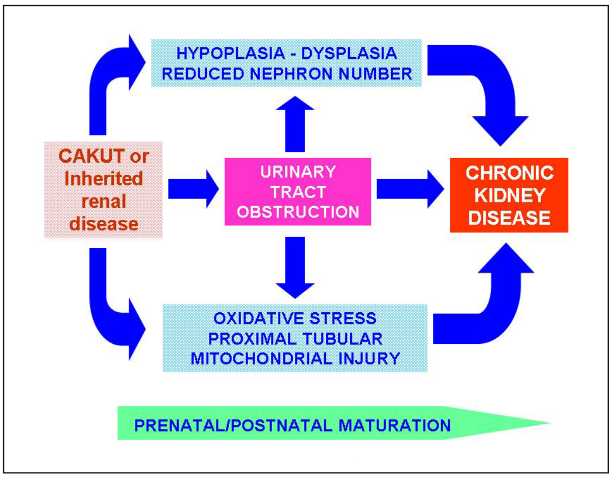

Figure 1. Major etiologies of congenital renal disorders: congenital anomalies of kidneys and urinary tract (CAKUT) and inherited renal disease, showing pathways leading to chronic kidney disease. Urinary tract obstruction can result directly from CAKUT. Continued obstruction, in turn, can lead to chronic kidney disease through proximal tubular oxidative injury aggravated by underlying renal developmental anomalies. Urinary tract obstruction can slow renal maturation, and the renal response to obstruction is in turn modulated by maturation.

with decreased nephron number at birth. Abnormal development of the urinary tract can interfere with nephron development and causes further loss of nephrons through proximal tubular injury. This occurs through oxidative stress and mitochondrial injury resulting from interference with oxidative metabolism in mature proximal tubular cells. The immature kidney appears to be initially resistant to obstructive injury, although urinary tract obstruction delays nephron development and maturation.

Therapeutic considerations

The molecular pathogenesis of obstructive nephropathy has been largely elucidated, and involves tubular injury, with secondary renal interstitial responses (**Fig. 2**) [14]. Numerous studies have pointed to the central role of the renin-angiotensin system and of transforming growth factor-β1 (TGF-β1) in the progression of kidney disease, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers are currently the primary agents available for clinical use. Whereas angiotensin inhibition may be effective in slowing the progression of chronic kidney disease in adults, their use in the neonate or infant may be problematic. Administration of these compounds to neonatal rats subjected to UUO actually aggravated the renal lesions by interfering with normal nephron

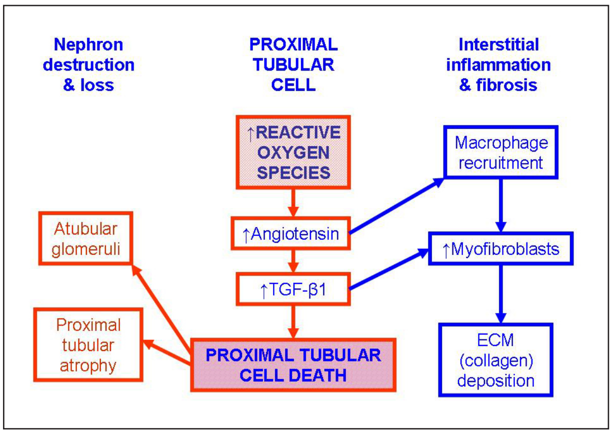

Figure 2. Pathways to renal injury resulting from urinary tract obstruction. Chronic urinary tract obstruction stimulates the production of reactive oxygen species, which increases production of angiotensin and transforming growth factor-β1 (TGF-β1), promoting tubular cell death. These events lead to tubular atrophy and the formation of atubular glomeruli. Cytokine production by proximal tubular cells induces recruitment of macrophages in the interstitium as well as the activation of interstitial fibroblasts to myofibroblasts, which lead to increased deposition of extracellular matrix (ECM) in the interstitium.

maturation [15]. Similarly, inhibition of TGF-β1 reduced proximal tubular injury and preserved renal parenchyma following UUO in adult mice, but aggravated renal parenchymal injury in neonatal mice with UUO [16].

The central role of proximal tubular mitochondrial injury in progression of congenital and heritable renal disorders suggests that antioxidant therapies may be effective. The challenge is to direct the antioxidant to mitochondria – this involves penetration of the agent across the cell membrane and sequestration in mitochondria to limit its toxicity and breakdown [17]. We are currently testing in murine models of UUO and cystinosis the efficacy of a compound conjugated to a lipophilic cation that can be concentrated in the mitochondria > 100-fold plasma concentrations. A shift in therapeutic target from collagen deposition in the renal interstitium to proximal tubular oxidative injury may preserve proximal tubular mass, at an earlier stage of progression. Preservation of nephrons is particularly important for infants with congenital nephropathies, as they are born with reduced nephron number, which cannot be regenerated.

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Declaration of interest

The Author declares that there is no conflict of interest.

References

1. Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A. Chronic renal insufficiency in children: The 2001 annual report of the NAPRTCS. Pediatr Nephrol. 2003;18:796-804.
2. Sweeney WE Jr, Avner ED. Diagnosis and treatment of childhood polycystic kidney disease. Pediatr Nephrol. 2011;26:675-92.
3. Wilmer MJ, Emma F, Levtchenko EN. The pathogenesis of cystinosis: mechanisms beyond cystine accumulation. Am J Physiol. 2010;299:F905-16.
4. Fetterman GH, Shuplock NA, Philipp FJ, Gregg HS. The growth and maturation of human glomeruli and proximal convolutions from term to adulthood. Studies by microdissection. Pediatrics. 1965;35:601-19.
5. Dicker SE, Shirley DG. Rates of oxygen consumption and of anaerobic glycolysis in renal cortex and medulla of adult and new-born rats and guinea-pigs. J Physiol. 1971;212:235-43.
6. Luyckx VA, Bertram JF, Brenner BM, Fall C, Hoy WE, Ozanne SE, Vikse BE. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. Lancet. 2013;382:273-83.
7. Eddy AA. Molecular basis of renal fibrosis. Pediatr Nephrol. 2000;15:290-301.
8. Forbes MS, Thornhill BA, Minor JJ, Gordon KA, Galarreta CI, Chevalier RL. Fight-or-flight: murine unilateral ureteral obstruction causes extensive proximal tubular degeneration, collecting duct dilatation, and minimal fibrosis. Am J Physiol Renal Physiol. 2012;303:F120-9.
9. Forbes MS, Thornhill BA, Chevalier RL. Proximal tubular injury and rapid formation of atubular glomeruli in mice with unilateral ureteral obstruction: A new look at an old model. Am J Physiol Renal Physiol. 2011;301:F110-7.
10. Forbes MS, Thornhill BA, Minor JJ, Gordon KA, Galarreta CI, Chevalier RL. The neonatal glomerulotubular junction is protected from obstructive renal injury until nephron maturation is complete. Pediatric Academic Societies Meeting 2013; Washington, DC. [Abstract 3810.212].
11. Upadhya P. Models of polycystic kidney disease. Meth Mol Med. 2002;86:13-25.
12. Galarreta CI, Grantham JJ, Forbes MS, Maser RL, Wallace DP, Chevalier RL. The role of tubular obstruction, progressive glomerulotubular injury, and formation of atubular glomeruli in murine models of neonatal and adult onset polycystic kidney disease. Pediatric Academic Societies Meeting 2013; Washington, DC. [Abstract 3810.213].

13. Chevalier RL, Forbes MS, Galarreta CI, Gubler M-C, Antignac C, Nevo N. Formation of atubular glomeruli in a mouse model of nephropathic cystinosis. Pediatric Academic Societies Meeting 2012; Boston, MA. [Abstract 3275.3].
14. Chevalier RL, Thornhill BA, Forbes MS, Kiley SC. Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. Pediatr Nephrol. 2010;25:687-97.
15. Chevalier RL. Mechanisms of fetal and neonatal renal impairment by pharmacologic inhibition of angiotensin. Curr Med Chem. 2012;19:4572-80.
16. Galarreta CI, Thornhill BA, Forbes MS, Simpkins LN, Kim D-K, Chevalier RL. Transforming growth factor-beta 1 receptor inhibition preserves glomerulotubular integrity during ureteral obstruction in adults but worsens injury in neonatal mice. Am J Physiol Renal Physiol. 2013;304:F481-90.
17. Smith RA, Hartley RC, Murphy MP. Mitochondria-targeted small molecule therapeutics and probes. Antioxid Redox Signal. 2011;15:3021-38.