Glomerulosclerosis and hypoplasia—A common theme?

Glomerulosclerosis is a common pathological finding associated with the progressive decline in renal function that follows a variety of acute and chronic renal insults. The complex pathophysiology of glomerulosclerosis is triggered by changes in renal hemodynamics following the loss of functional nephrons [1]. It logically follows that a decreased number of nephrons at birth might be associated with an increased risk of glomerulosclerosis in adult life [2, 3]. Indeed, children with oligomeganephronia, an uncommon disease characterized by as much as an 80% reduction in nephron number at birth, generally experience early progression to end-stage renal failure [4].

In addition to oligomeganephronia, a number of syndromes associated with renal aplasia, hypoplasia, and dysplasia lead to a congenital reduction in nephron mass [5]. Epidemiologically, multiple factors have been associated with decreased nephron formation, including low placental weight, low birth weight, and exposure to toxins in utero. Nephrogenesis is a complex, coordinated process of proliferation, cell death, morphogenetic patterning, and functional differentiation that is controlled by a tightly regulated program of specific gene expression [6]. Any perturbation of this well-orchestrated, developmental program can result in a reduced complement of nephrons at birth.

Although intrauterine exposure to certain toxins has been experimentally associated with abnormalities of kidney development, and reduced nephron number at birth has been associated with an increased susceptibility to glomerulosclerosis, these relationships are not consistent. There is significant variability in any given individual’s response to nephrotoxin exposure, and many individuals with reduced renal mass at birth do not develop progressive renal dysfunction as adults. Recent studies suggest that there are specific genetic factors which influence both a predisposition to in utero renal injury and glomerular scarring [7–9].

He et al demonstrated that genetic susceptibility to glomerulosclerosis was independent of reduction in nephron number by expressing the radiation-induced Os murine mutation (which results in oligosyndactyly and a congenital reduction in nephron number) on different genetic backgrounds [7]. While reduced nephron number, glomerular hypertrophy and cell turnover were identical in C57 Os/+ and ROP Os/+ mice, severe mesangial sclerosis was restricted to ROP Os/+ mice. In independent studies, Gilbert et al demonstrated that glomerular number was decreased in pups of female sclerosis-prone (Sprague-Dawley) rats that had received gentamicin from embryonic days 8–12 [8]. Most recently, in a productive collaborative effort reported in this issue of Kidney International, these two laboratory groups joined forces to determine whether there was a relationship between increased susceptibility to glomerulosclerosis and increased fetal susceptibility to a commonly used nephrotoxin, gentamicin [9]. Using a well-designed set of in vivo and in vitro experiments, they determined that ureteric bud branching and glomerular formation were decreased in sclerosis-prone (ROP +/+), but not sclerosis-resistant (C57 B1/6) mice following intrauterine gentamicin exposure. Although this study did not address specific mechanisms, the data presented suggest that there is an association between susceptibility to glomerulosclerosis in adulthood and reduction in nephron number in utero. The authors conclude that “…exposure to nephrotoxins in utero compounds the risk of renal failure as an adult in sclerosis-prone individuals” [9].

But what is the genotype of a sclerosis-prone individual? What are the common genetic features of individuals risk of severe renal developmental abnormalities with in utero nephrotoxin exposure and those who are predisposed to glomerulosclerosis following a variety of insults? The answers to these questions await clear delineation of the genetic basis for abnormal kidney development and glomerulosclerosis. New molecular technologies permit exciting and innovative approaches to such questions. The development of high throughput, automated applications of chip-based gene and protein expression technology will permit the identification of specific genetic profiles of renal disease pathophysiology and susceptibility [10]. For now, one can only speculate about possible interactions of the pathways regulating nephron formation and glomerulosclerosis. Common pathophysiological intermediates identified to date include members of the TGF-β superfamily and angiotensin II [1, 6].

The clinician can look forward to a brave new world where nephron preservation therapies are individually tailored for specific genetic susceptibility profiles. Until then we must be content to minimize exposure to...
nephrotoxins and further explore the possibilities of altering the progression of established renal injury with renoprotective regimens, including dietary manipulation and aggressive control of blood pressure and proteinuria.

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REFERENCES