EDITORIAL

Congenital ureteral obstruction: New technology, new targets

Chronic kidney disease in childhood most often stems from congenital abnormalities of the urinary tract. Among these, obstructive uropathy is most common, accounting for approximately 16% of all cases of end-stage renal disease (ESRD) in children [1]. Over the past several decades, with the availability of antenatal detection of fetal anomalies, early intervention has become a goal; early postnatal intervention to relieve genitourinary obstruction has become routine (and intrauterine intervention, occasional). However, correction of urinary tract obstruction has turned out to be insufficient, per se, in preventing progression of renal dysfunction in a substantial number of children with obstruction. Consequently, research aimed at solving the puzzle as to why this is so has occupied many investigators [2–5]. Despite a large body of clinical and experimental data, many aspects of obstructive uropathy and why it progresses remain unsolved. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has recently released a program announcement, PA-03-076, on this subject, entitled “Basic and clinical studies of congenital urinary tract obstruction,” with the express purpose of stimulating “novel and productive research focusing on congenital urinary tract obstruction [6].”

A number of experimental models in several species have been utilized to delineate the course of obstructive uropathy, both surgically induced and spontaneous [2–4, 7–10]. Among these, unilateral ureteral obstruction (UUO) in the neonatal rat has been a widely studied model, as producing the lesion is straightforward, if technically demanding. UUO is an attractive model, since nephrogenesis in the rat extends throughout the first postnatal weeks. An issue with this model, however, is the fact that onset of obstruction is surgical, and most human cases of obstructive uropathy are not of such sudden onset. Thus, models in which onset is spontaneous [4] also have appeal, though these are less completely studied. Irrespective of the model, a final common pathway seems to be progression of renal dysfunction over time, even after obstruction has been relieved.

There is consensus that severe obstructive uropathy interferes with renal development, a complex interaction of inductive events, communication between cells, and proliferation. The expression and function of number of candidate genes and systems are already known to be involved in congenital obstructive uropathy, for example, renin, angiotensin receptors, the kininogen family, transforming growth factor (TGF)-beta, epidermal growth factor (EGF), smooth muscle actin, heat shock protein-27, clusterin, NOS, endothelin, neuropeptide Y, and adrenomedullin, to mention a few [11–16]. Such genes have mainly been sought as candidate genes, largely based on their known functions. With the completion of the human genome project and the advent of high throughput techniques such as array technology, it is possible to cast a wider net to find other genes with altered expression. Indeed, such new technology can both confirm the previously observed, and, more interestingly, help in developing testable hypotheses. The amount of data, nevertheless, is very large indeed. For example, recently, Stuart et al [17] examined changes in gene expression patterns during multiple points of development and maturation of the rat kidney, and reported that 873 of 8740 genes included in the Affymetrix U34A gene chips varied with the developmental stage.

In this issue of *Kidney International*, by employing DNA array technology, Silverstein et al [18] present results that are both hypothesis confirming and hypothesis generating. Despite some inevitable limitations of such work, the results bolster several concepts about congenital ureteral obstruction—that inflammation and immune modulation are important in the progression of obstructive uropathy, that genes that control cytoskeleton and extracellular matrix are affected in severe obstruction, and that multiple other genes are increased or decreased in their expression. The results are provocative and thus should be, among other things, hypothesis generating.

Results from studies utilizing array technology require confirmation by other techniques. While Silverstein et al [18] did not employ semi-quantitative or real-time reverse transcription polymerase chain reaction (RT-PCR), or Northern analysis to confirm levels of mRNA expression, they used Western analysis to assess involvement of the products of 10 immunoregulatory genes that appeared up-regulated on the array studies. They found increased protein expression of these genes of interest, strongly suggesting that the array findings had functional significance in their model.

Many of the findings of Silverstein et al [18] are confirmatory, which is reassuring, given the fact that the array they utilized contained genes already known to be involved in UUO. The authors report that they found an increase in a number of genes previously shown to have altered expression in neonatal UUO, including clusterin, EGF, HSP-27, renin, smooth muscle actin, and TGF-beta. They also observed increases or decreases in some 250 genes, some of which were not previously

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known to be involved in the process of UUO. Some of these genes fall into groups that should lead to further study and new hypotheses—genes that are involved in immunomodulation and inflammation, in cytoskeletal structure, in transport, and in fibrosis.

A finding of particular interest is that certain additional genes involved in immunomodulation and inflammation appear to be up-regulated in kidneys that have been obstructed for 12 days, denoted by the authors as chronic UUO. Though some of these genes were not previously reported as involved in experimental surgical UUO, the concept that inflammation and immune modulation is involved is not entirely new [19]. For example, it has been known for some time that interleukin-1 (IL-1) is involved in renal interstitial injury. Yamagishi et al [20] showed that genetically modified cells from bone marrow could be used as vehicles to deliver an IL-1 receptor antagonist and that this ameliorated the inflammation in renal interstitium of mice with UUO. Work by Isaka et al [21] has shown that antisense oligodeoxynucleotides can block interstitial fibrosis in UUO.

Silverstein et al [18] looked at two time points: four days for “acute” UUO and 12 for “chronic” UUO and observed that over 250 genes were either up-regulated or down-regulated. Thus, particularly early events, for example, those that might occur within the first 24 hours after obstruction, were not included, and a more complete time course would be interesting and important to delineate. The authors are aware and have previously reported that during critical periods of nephrogenesis, ureteral obstruction causes impaired growth of the obstructed kidney and stimulates compensatory growth of the opposite kidney in a pattern directly proportional to the duration of the obstruction.

What do the results of the present study tell us? First, that there are other systems to examine besides those that have already been studied. Immune modulators that affect fibrosis are important, and this present study suggests some further mediators to consider. Such results, in combination with studies such as that of Yokoyama et al [22], who reported that ADAMTS-null mutant mice develop kidney lesions that look like obstructive uropathy, should make it possible to turn our attention to methods to interrupt fibrogenesis in novel ways.

Second, the results show that the expression of certain transporter and tubular regulatory genes are decreased after 12 days of obstruction, perhaps suggesting further reasons behind the disordered fluid handling that occurs with marked obstruction.

Finally, the results serve to remind one that by trawling, one does catch fish. The power of high throughput technology, and accompanying powerful analytic tools, is the extensive data through which one can sort. The promise is the possibility of a big catch, if one knows where to fish.

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