Genetic factors in progressive renal disease: the good ones, the bad ones and the ugly ducklings

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disease susceptibility may increase the understanding of the pathogenesis of ESRD. The regenerative effects of endogenous molecules in the kidney may be exploited to counteract the growing incidence of ESRD efficiently.

Genetic factors in kidney diseases

In some cases, the relationship between genetics and renal disease development is evident. Examples are familial forms of focal and segmental glomerulosclerosis that are caused by mutations in the podocyte molecules podocin, CD2-associated protein, α-actinin-4 or the canonical transient receptor potential 6 [1–4]. Screening for mutations in the above-mentioned genes in sporadic cases of nephrotic syndrome has provided new insights and is increasingly being integrated in paediatric nephrology [5].

Genetic factors frequently have a less direct influence on renal disease development and become manifest only in the presence of ‘permissive conditions’ such as diabetes mellitus and hypertension. Conversely, not all patients suffering from these conditions develop renal disease or progress to ESRD, and it is likely that genetic factors determine the time of onset and the rate of progression of the kidney disease. Several studies of genetic linkage analyses in diabetic nephropathy have shown a susceptibility locus on chromosome 18q [6,7]. A polymorphism in the DNA sequence of the CNDP1 gene, which encodes the enzyme carnosinase-1, on chromosome 18q in diabetic patients determines susceptibility to develop diabetic nephropathy [8].
The substrate of carnosinase-1, L-carnosine, is a potent inhibitor of oxidative stress [9] and the formation of advanced glycation end-products [10], and may thus act as a cytoprotective factor during diabetes. It was postulated that opposing mechanisms, i.e. hyperglycaemia vs the action of protective factors such as L-carnosine, determine the net outcome of diabetic nephropathy [8]. The importance of genetic predisposition to renal disease is emphasized further by the fact that individuals with a family history of ESRD have a higher risk of ESRD [11].

Genetic factors also appear to play a role in transplantation. The influence of donor tissue characteristics on prognosis in kidney transplantation has been investigated by comparing the functionality of two kidneys from one donor in different recipients. In a large cohort of paired donor kidneys, graft function and survival of one graft could be predicted by the performance of its ‘mate’ graft [12]. The data may suggest that, among other factors, the repair capacity of the graft tissue has an influence on the post-transplant course. The hypothesis that the repair capacity of the graft tissue is at least partly genetically determined is supported by observations that polymorphisms in cytokine genes of the donor are associated with long-term graft survival in the recipient [13].

Genetic predisposition to renal disease in animal models

The natural genetic heterogeneity among individuals impedes the identification of genes marking a predisposition to progressive renal disease in humans. Investigation of animal models, through comparison of strains that are progressors with those that are not, may circumvent these problems. Identified candidate genes in animal models could eventually be of relevance in human populations. An animal model for human immunodeficiency virus (HIV)-associated nephropathy has been used successfully to identify disease susceptibility loci that may be of importance for human renal diseases. With linkage analysis in HIV-transgenic mouse strains, Gharavi et al. found a locus on chromosome 3 which was associated with renal damage [14]. This locus corresponds to the human chromosome 3q25–27, which has been linked to various causes of ESRD [15,16].

Genetic linkage analyses in rats have led to the identification of chromosomal loci associated with the development of glomerular lesions, hypertension, albuminuria and proteinuria [17–19]. Two Lewis rat substrains with small genetic differences but with considerable difference in susceptibility to develop progressive glomerulosclerosis after induction of anti-Thy-1 glomerulonephritis have been identified [20]. Kidney and bone marrow transplantation experiments performed in our laboratory showed that predisposition to progressive glomerulosclerosis is governed by genes expressed in the kidney, but not by genes expressed in bone marrow-derived cells [21]. Similar experiments are being conducted in this model to localize genes that cause a predisposition to proteinuria.

Since chromosomal regions identified by linkage analyses generally contain tens to hundreds of genes, pinpointing the exact genes that are affected in the case of one particular disease is an elaborate task. Mutations in the DNA sequence of such genes may give rise to altered gene expression levels. Therefore, an alternative approach for the identification of genes involved in progression or remodelling of damage to the renal tissue is the application of genome-wide gene expression analysis with microarray. Identification of genes determining disease progression will benefit from the combined application of genetic linkage analysis and gene expression profiling [22].

Regeneration capacity of the kidney

Several studies support the concept that the kidney has a natural capacity to remodel into its original architecture after injury. In patients with type 1 diabetes and diabetic nephropathy, 10 years of normoglycaemia after pancreas transplantation resulted in amelioration of glomerular and tubular lesions in the kidney [23]. Administration of an angiotensin II receptor antagonist to hypertensive rats led to regression of renal vascular and glomerular fibrosis [24]. The molecular mechanisms governing regression of renal lesions are not yet clear. Therefore, it is useful to investigate these mechanisms, since knowledge about them might contribute to the development of therapies that target the endogenous molecular pathways to prevent or even reverse renal damage.

In this respect, heme oxygenase-1 (HO-1) is a promising example. This molecule displays cytoprotective activity: due to its protection against tissue damage, HO-1 upregulation is a beneficial response after acute renal injury [25]. A polymorphism in the promoter region of the donor’s HO-1 gene, which influences the level of expression, has been associated with graft survival [26,27]. Another protein that might be able to protect the kidney against permanent damage is bone morphogenic protein-7 (BMP-7). This molecule plays a central role in kidney embryogenesis and maintenance of the tubular epithelial phenotype. BMP-7 impedes myofibroblast formation and reverses chronic renal injury, which demonstrates that recombinant BMP-7 may be a novel treatment opportunity in chronic renal disease [28]. The prolactin receptor (PRLR) may be a novel endogenous molecule capable of protecting the kidney against damage. Gene expression profiling showed that PRLR, like BMP-7, is abundantly expressed in the cortices of normal kidneys [29]. After 6 months, PRLR mRNA levels were 30 times lower in patients that would show chronic allograft nephropathy after 12 months than in patients that would have retained normal morphology after 12 months [30]. The data may suggest that PRLR is an intrinsic factor in the protection of the kidney against permanent
damage. Novel data show that in kidney transplants with rejection, decreasing expression levels of PRLR are accompanied by an increase in the extent of fibrosis (Figure 1).

It is important to find out why protective and regenerative mechanisms function in some patients, but fail in others. The question of whether gene polymorphisms determine the expression levels of potential cytoprotective proteins such as BMP-7 and PRLR also requires an answer.

**Conclusion**

Genetic linkage analyses in patients and animal models have led to the identification of chromosomal regions that are associated with renal disease. Genes located in such chromosomal regions may predispose a patient to progression of the kidney disease or, alternatively, induce regeneration mechanisms in damaged renal tissue. Indeed, there is convincing evidence for the existence of endogenous molecules that protect the kidney against permanent damage. Identification of genes involved in progressive renal disease will lead to a better understanding of the pathophysiology of kidney diseases. Elucidation of the regulation of the expression of cytoprotective molecules might result in improved therapies that exploit endogenous protective and regenerative mechanisms.

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**References**


Role of inflammatory cells in the kidney in the induction and maintenance of hypertension

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"Two forms of inflammation can be separated from one another; the purely parenchymatous inflammation, where the process runs its course in the interior of the tissue... and the secretory (exudative) inflammation where an increased escape of fluid takes place from the blood... Every parenchymatous inflammation has from its outset a tendency to alter the histological and functional character of an organ". Rudolf Virchow (1860).

Introduction

The incidence of hypertension has increased dramatically in the last decade [1]. While the relative importance of environmental, congenital and genetic factors have been extensively debated, there is a general agreement that, whatever the cause, there is a