Role of the immune system in the pathogenesis of idiopathic nephrotic syndrome

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ABSTRACT

Idiopathic NS (nephrotic syndrome) is characterized by massive proteinuria, due to a leak in the glomerular barrier to proteins. Genetic defects that affect the function and the composition of the glomerular capillary wall, in particular of the visceral epithelial cells, have recently been recognized as the cause of familial forms of NS. MCNS (minimal change NS) and FSGS (focal and segmental glomerulosclerosis) are common non-familial forms of NS in which the causative defect has not yet been identified. Several studies have shown that non-familial NS is associated with the presence of circulating permeability factors and with complex disturbances in the immune system. Thus far, there is no direct evidence that these factors directly alter glomerular permeability to proteins, and some of these factors may be a consequence, rather than a cause, of NS. In this review, we will briefly highlight the mechanisms that underlie proteinuria in general and focus on the immunological disturbances associated with idiopathic NS, with attention to potential mechanisms whereby the immune system may directly act on the glomerular capillary filter.

INTRODUCTION

Urine is practically devoid of high-molecular mass proteins, which is achieved by the sieving characteristics of the glomerular filtration barrier and by resorption of proteins in the proximal tubules of the kidney. Many glomerular diseases result in a pathological increase in glomerular permeability to proteins. If proteinuria exceeds 40 mg·m⁻²·h⁻¹, hypoalbuminaemia accompanied by oedema will ensue. The clinical picture of proteinuria, hypoalbuminaemia and oedema is referred to as ‘nephrotic syndrome’ (NS).

The term ‘idiopathic’ NS is often used to describe a heterogeneous group of proteinuric glomerulopathies that occur predominantly in children. Over the last few years it has become recognized that some forms of NS formerly assigned as ‘idiopathic’ NS are caused by mutations in genes that encode structural components of the glomerular filter (as reviewed in [1]). Although mainly familial, sporadic cases of these diseases have been described [2,3]. Clinically, they are characterized by therapy-resistance and eventual progression to end-stage renal failure.

Non-familial forms of NS are more common. Based on the renal biopsy findings, non-familial idiopathic NS can be grossly subdivided into MCNS (minimal change NS) and FSGS (focal segmental glomerulosclerosis). As indicated by its name, renal tissue from MCNS patients shows no changes under light microscopy. More explicitly, there are no signs of inflammation, immune complex deposition or sclerosis. FSGS is characterized by collapse of the glomerular capillaries with sclerosis and hyalinosis and the formation of adhesions of the glomerular tuft.

Advances in the field of molecular biology have enabled the elucidation of the causes of various familial
forms of NS in the late 1990s. Concomitant, this has provided a wealth of information on the molecular make-up of the glomerular filtration barrier. In contrast with these rapid advances in the field of hereditary NS, our insight in the pathogenesis of non-familial NS is still limited. In this review, we discuss the aetiology of non-familial idiopathic NS, focusing mainly on the possible role of immunological factors.

**MCNS**

In children, MCNS is the most common form of NS, accounting for 35–80% of the cases of NS, depending on ethnicity [4–9]. In adults, MCNS is the third most common form of NS, next to membranous nephropathy and FSGS, accounting for 15–25% of the cases of unexplained adult NS [10]. MCNS is more common in Hispanics, Asians, Arabs and Caucasians than in African-Americans [9,11–14]. Depending on race, the reported incidence of MCNS varies from 2–16 per 100,000 children under 16 years of age [11,15–17]. Previous studies report higher incidences of MCNS than more recent studies do, probably because the incidence of FSGS has increased over time while the incidence of MCNS may be decreasing [9,10,18].

Clinically, MCNS is characterized by highly selective proteinuria, i.e. mainly albuminuria, which generally responds well to treatment with corticosteroids. Approx. 90% of children with MCNS and up to 70% of adult patients will respond with a complete remission to a course of corticosteroids [7,19], yet are prone to relapse. Relapses are most frequent in children. In a follow up study, 95% of children with biopsy-proven MCNS relapsed during 17 years follow-up [20]. Lower relapse rates have been reported, depending on the therapy regimen [21,22]. If responsive to steroids, the outcome of the disease is excellent. Long-term studies with a follow-up of up to 20 years have shown that practically none of the children with steroid-sensitive biopsy-proven MCNS develop hypertension, loss of renal function or FSGS [20,23,24]. In adults, the outcome is similar [25–27]. Therefore MCNS is often referred to as steroid-sensitive NS.

In frequently relapsing patients and in steroid-dependent patients, prolonged or repeated steroid therapy can lead to a variety of serious side effects. In these patients, alternative therapeutic strategies can be used to induce long-lasting remission. These include other drugs that modulate the immune system, such as cyclosporine [28–31] and levamisole [32–35], and alkylating agents, such as cyclophosphamide [36–38] and chlorambucil [39].

**FSGS**

FSGS is a non-specific pattern of glomerular injury that is frequently encountered in human renal biopsies. In adults, only some cases represent idiopathic FSGS, whereas, in children, almost all cases are idiopathic. Clinically, FSGS is characterized by increased urinary protein excretion and decreasing kidney function. In idiopathic FSGS, proteinuria is massive and associated with NS. In non-idiopathic forms, FSGS develops secondary to other processes that affect the glomerulus, such as hyperfiltration and hypertension, or scarring following inflammatory, proliferative or thrombotic glomerulopathies; usually, these cases present with less extensive proteinuria [18]. The incidence of idiopathic FSGS has progressively increased and FSGS now constitutes the most frequent diagnosis in native adult kidneys, accounting for 35–50% of cases of adult NS, depending on race [10]. In children, FSGS is the second most frequent cause of idiopathic NS, accounting for 20–32% of NS [40]. The diagnosis of idiopathic FSGS is most frequent in African–Americans. It has become clear that a significant proportion of children with steroid-resistant FSGS, both familial and non-familial, have mutations in the gene that encodes for the podocyte protein podocin [2,3]. The large heterogeneity of the disease is illustrated by the various responses to treatment with corticosteroids. Idiopathic FSGS, both in children and in adults, may respond to corticosteroids [41,42], yet many patients show steroid-dependence [43,44]. Steroid-dependent and steroid-unresponsive patients may benefit from treatment with cyclosporine or cyclophosphamide [43–48]. However, more prolonged therapy than in MCNS is generally required to induce remission.

Progression of FSGS lesions leads to renal insufficiency and finally to end-stage renal failure, requiring renal replacement therapy. Upon transplantation, the disease relapses in 20–50% of patients [49,50].

**MCNS AND FSGS: ONE DISEASE?**

There has been a long debate as to whether or not MCNS can evolve into FSGS. There have been reports on some cases of NS in children who were initially corticosteroid responsive with presumed MCNS histology, but later progressed to renal failure [51]. Ahmad and Tejani [52] reported that, in more than 50% of 49 MCNS patients, the renal disease evolved into FSGS over a 10-year period of repeated renal biopsies. However, the natural history of MCNS and FSGS is often hard to define, since only a few children undergo initial renal biopsy before corticosteroid treatment is started [20]. It has been suggested that long-standing proteinuria may contribute to the transformation of MCNS to FSGS [53]. Studies on familial NS would support the hypothesis that MCNS and FSGS are part of the same disease spectrum [54], since patients with the same genetic defect exhibit a range of pathologies from minimal changes to FSGS [2]. Altogether, it is still unclear whether MCNS and FSGS are aetiologically related. In this review, we
will discuss the pathogenesis of both MCNS and FSGS as separate entities.

THE GLOMERULAR CAPILLARY WALL

The glomerular filtration barrier consists of three layers: (i) the endothelium lining the inner side of the glomerular capillaries; (ii) the GBM (glomerular basement membrane), and (iii) the glomerular visceral epithelial cells or podocytes that cover the outer side of the glomerular capillary loops. Podocytes are polarized differentiated cells, which owe their name to their complex shape that appears to be designed to allow ultrafiltration. The cell bodies have numerous primary, secondary and tertiary extensions, the latter called foot processes or peduncles. The foot processes cover the GBM in an interdigitating pattern, so that adjacent foot processes are derived from different epithelial cells (Figure 1A). On the basal side, the foot processes adhere to the GBM. Laterally, the foot processes are interconnected by slit diaphragms through which the filtration route is arranged (Figure 1B). The apical side of foot processes extends into the urinary space.

PODOCYTE INJURY IN NS

NS is associated with dramatic changes in podocyte architecture, as detected by electron microscopy. These changes consist of loss or effacement of the podocyte foot processes (Figures 1C and 1D) and suggest a process of transdifferentiation. The precise mechanism underlying podocyte foot process effacement and its relationship to proteinuria are not fully understood.

As stated above, the genetic basis for several forms of hereditary NS has been solved recently, and the causative genes indeed appear to affect a single cell type: the podocyte. Briefly, these diseases include congenital NS of the Finnish type, autosomal-recessive steroid-resistant NS, familial forms of FSGS, diffuse mesangial sclerosis associated with Denys–Drash syndrome and with Frasier syndrome, and NS associated with nail-patella syndrome. Studies on genetically modified mice have confirmed that proteinuria associated with podocyte dedifferentiation can be induced by disruption of single genes encoding proteins that appear indispensable for podocyte function. These proteins include molecules that locate at the slit diaphragm (nephrin, neph1, podocin, CD2AP and the Src family kinase Fyn), transcription factors (WT-1, Lmx1B, Podl and Krml1/MafB), cytoskeletal components (α-actinin-4 and RhoGDIα), adhesion molecules (α3 integrin) and components of the GBM (S-laminin/ laminin β2) (as reviewed in [55–57]).

Proteinuria and a distorted podocyte phenotype can be induced not only by intrinsic damage to podocytes, but also by extrinsic damage to podocytes. Studies in animal models have shown that injection of antibodies directed against podocyte epitopes, such as slit diaphragm components nephrin and neph1, the apically located epitopes podoplanin [58] and aminopeptidase A [59], and also against the GBM component heparan sulphate [60], cause immediate and massive proteinuria. In addition, podocyte damage by administration of puromycin aminonucleoside and adriamycin, which are compounds that are
directly toxic to podocytes, to experimental animals is associated with aselective proteinuria [61–65].

Taken together, proteinuria can be induced by several types of podocyte injury, including intrinsic and extrinsic damaging factors. The extensive effacement of podocyte foot processes as the hallmark of non-familial idiopathic NS suggests a pivotal role for the podocyte in the pathogenesis of these forms of NS. An intrinsic defect at any level in the glomerular filtration barrier may underlie these diseases, but this defect has thus far not been identified. Alternatively, podocyte injury in non-familial idiopathic NS may result from extrinsic damage caused by a circulating factor. The possible role of circulating factors has been favoured by many studies and will be addressed below.

CIRCULATING PERMEABILITY FACTORS

For FSGS, the involvement of a circulating permeability factor in its pathogenesis has been suggested by several lines of evidence. Proteinuria frequently recurs in the donor kidney of FSGS patients after receiving a non-FSGS kidney transplant [66–68]. However, it has been reported that proteinuria in two FSGS kidneys disappeared after transplantation in two recipients [69]. Likewise, in a rat model of FSGS, the spontaneously proteinuric Buffalo/Mna rat model, disease recurs in the donor kidney from healthy control rats transplanted into Buffalo/Mna recipients and proteinuria and renal lesions regress when the Buffalo/Mna kidneys are transplanted into normal control rats [70]. These data suggest that the FSGS kidney does not bear the causative defect. Also, the efficacy of plasmapheresis in the treatment of proteinuria in FSGS patients [71–74] and the transmission of proteinuria from an FSGS mother to her child during gestation [75] point to the presence of a causative factor in plasma. The latter is supported by experimental data showing the induction of albuminuria in rats upon intravenous administration of plasma from FSGS patients [76,77]. Also, serum from FSGS was shown to increase the permeability of isolated glomeruli to albumin in an in vitro system [78,79].

For MCNS, the involvement of a circulating permeability factor in the pathogenesis is less well established, due to the fact that MCNS by definition does not require renal transplantation and, therefore, clinical transfer studies are not present. In MCNS, the hypothesis of a pathogenic circulating factor is based merely on experimental data showing the induction of albuminuria in rats upon injection of culture supernatants of stimulated PBMC (peripheral blood mononuclear cells) from patients with MCNS [80–82] or of a factor produced by human T-cell hybridomas derived from an MCNS patient in relapse [83]. Also, the association of MCNS with lymphoproliferative disease, in particular Hodgkin’s disease [84,85], T-cell lymphoma [86] and thymoma [87], and the induction of remission by removal of the tumour suggested that circulating factors might play a causal role in the mechanism of proteinuria.

Several candidate permeability factors have been identified to date; however, most have only been partially characterized biochemically. Some of these factors are not entirely specific for any particular glomerular lesion causing NS. Also, it is still unknown what would be the constituent of the glomerular capillary wall that represents the target of such permeability factors [88]. Yet, the data presented above suggest that a putative circulating factor in MCNS would be produced by PBMC or, more specifically, T-cells, pointing to a role of the immune system.

ROLE OF THE IMMUNE SYSTEM

Association of NS with atopy

In 1974, Shalhoub [89] proposed that MCNS was a disorder of lymphocyte function with increased levels of a lymphocyte-derived permeability factor. This hypothesis was based on several clinical observations that suggested the involvement of the immune system in the pathogenesis of idiopathic NS. In 1959, Hardwicke et al. [90] first reported on a patient with NS in association with pollen hypersensitivity. Since then, many reports have been published on patients who developed NS after having experienced allergic reactions to inhaled allergens [91–96], vaccinations [97,98], food [95,99–103] and insect stings [104,105]. Furthermore, the incidence of atopy was reportedly higher in patients with idiopathic NS than in healthy subjects, ranging from 17–40 % in MCNS patients compared with 10–23 % in age-matched control subjects [106–112].

It should be remembered that there is no standard definition of the entity ‘atopy’, that its prevalence varies between populations and countries and, therefore, that there is no official number on the prevalence of ‘atopy’ in the general paediatric population. Also, the incidence of allergic reactions in children is high and a causal relationship between allergic events and NS is hard to prove. Reservations should also be made for intervention studies that aim at the value of dietary interventions or anti-allergic regimens in the treatment of NS. Some investigators have shown that oligoantigenic diets, in addition to immunosuppressive therapy, contributed to achieve remission in some patients [103,113]; however, others found no effect of anti-allergic regimens in NS [114,115]. Here, the conflicting results may be explained by the large heterogeneity of the disease, its various responses to treatment with corticosteroids and uncertainty as to its natural course.

Allergy is associated with an elevated production of IgE by B-lymphocytes, and several investigators have reported an elevation of IgE in the serum of NS patients.
κet al. [121] showed high levels of NF-κB, which was not observed in healthy controls. Sahali et al. showed clonally expanded T-cells of idiopathic NS patients and compared with controls. Peripheral blood, PBMC or subsets of T-cells were collected from patients with idiopathic NS and compared with control patients. Frank et al. [120] showed that CD8-positive T-cells of idiopathic NS patients are clonally expanded, which was not observed in healthy controls. Sahali et al. [121] showed high levels of NF-κB (nuclear factor κB) DNA-binding activity in T-cells from untreated MCNS patients during relapse compared with the MCNS patients in remission while treated with immunosuppressants. This all points to activation of the T-cells in MCNS.

Other workers have focused on the production of cytokines by PBMC or T-lymphocytes. Cytokines are small proteins (molecular mass of approx. 8–80 kDa) that function as soluble mediators in an autocrine or paracrine manner. Cytokines are produced by both immune cells and non-immune cells, and their targets also include both immune and non-immune cells. Based on their profile of cytokine production, Th-helper lymphocytes can be divided into Th1 and Th2 cells. Th1 cells typically produce IFN-γ (interferon-γ), TNF (tumour necrosis factor)-β and IL (interleukin)-2, which activate cytotoxic and inflammatory reactions. By contrast, Th2 cells produce IL-4, IL-5, IL-9, IL-10 and IL-13, which are associated with the regulation of strong antibody and allergic responses [122,123]. For instance, in asthma, cytokines IL-10 and IL-13, produced by activated Th2 lymphocytes, act directly on pulmonary fibroblasts and bronchial epithelium and thereby cause an important part of the phenotype [124–127].

Studies on in vitro mitogen-stimulated production of cytokines by PBMC from patients with idiopathic NS have demonstrated an increased production of various cytokines, including IL-1 [128], IL-2 [128,129], IL-4 [129,130] and TNF-α [131], compared with patients in remission or with healthy controls. Matsumoto et al. [132,133] and Matsumoto and Kanmatsuse [134,135] reported a decreased production of IL-1 and IL-10 by PBMC from MCNS patients and increased production of IL-12 and IL-18 compared with normal controls. To circumvent artefacts induced by stimulation with mitogens, Kimata et al. [136] studied the unstimulated production of cytokines by T-lymphocytes of MCNS patients and found an increased production of IL-13, whereas production of IL-4 was normal. An elevated expression of IL-13 mRNA was shown by Yap et al. [137] using a semi-quantitative RT (reverse transcriptase)-PCR technique; this was associated with decreased expression of TNF-α and CD14 in monocytes [138]. It has been shown that the increased expression of IL-13 was not related to known polymorphisms in the IL-13 gene [139] or in the genes encoding the transmembrane receptors for IL-4 and IL-13 [140,141].

The studies mentioned above all investigated only a set of preselected cytokines. Using a subtractive cDNA library screening technique, Sahali et al. [142] applied an unbiased technique and reported differential expression of transcripts involved in the T-cell receptor-mediated complex signalling cascade and a decreased expression of IL-12 receptor β2 mRNA by PBMC in untreated MCNS patients during relapse compared with MCNS patients in remission.

The studies described here not only reveal the involvement of T-cells in the pathogenesis of idiopathic NS and, more specifically, Th2-mediated immunity, they also illustrate the difficulties that are encountered when studying samples of patients with idiopathic NS. It is difficult to obtain a homogeneous patient group. At the time of presentation, the duration of proteinuria varies and some patients may have already started treatment. Treatment with immunosuppressive drugs will affect not only the production of the presumed permeability factor, but also of many other factors that are not involved in the disease. Furthermore, it may be difficult to select a correct control group, which would ideally consist of the same NS patients when in remission and not taking any medication; this may seem most feasible in the frequently-relapsing patients, yet these patients are often steroid-dependent. Also, in the nephrotic state, the composition of circulating blood changes, with hyperlipidaemia as a common and hazardous complication. This altered state itself may activate the immune system, as shown by Lenarsky et al. [143], who reported that the presumed immunosuppressive effect of serum of nephrotic patients, which had been claimed before, could be reversed simply by removal of the lipoprotein fraction. Thus hyperlipidaemia itself modulates the immune system and may also alter the production of circulating factors, which may be easily misinterpreted as permeability factors.

The difficulties mentioned above are illustrated by a recent study in our laboratory (J. G. van den Berg, unpublished work). By quantitative real-time PCR, we studied the expression of IL-1β, IL-1α (IL-1 receptor antagonist), IL-2, IL-4, IL-5, IL-9, IL-10, IL-13, TNF-α, and IFN-γ by PBMC from patients with MCNS during relapse and remission and from a control group of patients with NS primarily caused by endogenous alterations within the glomerular filter, for instance mutations in the genes encoding nephrin and podocin. Out of the cytokines studied, only the expression of IL-10 and IL-13 mRNA was significantly up-regulated in relapsing MCNS patients when compared with MCNS patients in remission. The expression of IL-13 mRNA, however, was also up-regulated in the nephrotic control group. The results are shown in Figure 2, and clearly...
Figure 2  Expression of IL-10 in patients with MCNS
mRNA expression of IL-10 (A) and IL-13 (B) by PBMC from MCNS patients during relapse (n = 15) and in remission (n = 15), and from a control group of patients with NS primarily caused by endogenous alterations within the glomerular filter (n = 7), as detected by quantitative real-time PCR. Values are expressed relative to the mRNA levels of the house-keeping gene β-actin, in arbitrary units. All patients were free of immunosuppressive drugs for at least 3 weeks. (C) Plasma IL-10 levels in the same patients, as detected by ELISA. Horizontal lines denote median values. Kruskal–Wallis tests and Mann–Whitney tests were applied to evaluate differences between the patient groups.

illustrate the heterogeneity of the patient groups studied; approximately half of the patients had up-regulation of the particular cytokine.

Response to immunosuppressive drugs
The favourable response of NS to immunosuppressive drugs in most patients has been regarded as additional proof of the involvement of the immune system in the pathogenesis of NS. Interestingly, levamisole is a potent down-regulator, specifically of Th2 immune responses, whereas it augments Th1 responses [144]. The beneficial effect of levamisole would again advocate the role for Th2-mediated immune responses in the pathogenesis of NS. However, the efficacy of immunomodulatory drugs may be explained by another mechanism, i.e. by direct effects on the glomerular capillary filter. For example, both podocytes and endothelial cells express glucocorticoid receptors through which corticosteroids may exert direct actions on the glomerular capillary wall [145,146].

Direct damage to the glomerular capillary wall by cytokines
As stated above, there is no significant influx of inflammatory cells into glomeruli of patients with idiopathic NS and there are no signs of immune complex deposition. The activation state of T-cells in nephrotic patients, as described above, thus does not result in inflammatory events at the glomerular capillary wall. However, cytokines and other circulating factors may be able to act directly on the glomerular capillary wall. These interactions may take place via cell-surface receptors.

The podocyte is equipped with cell-surface receptors at the basal cell membrane. These receptors include α3β1 integrin with CD151 and integrin-linked kinase [147–149], and the dystroglycan complex [150,151]. These adhesion receptor complexes are linked to the submembranous actin cytoskeleton and mediate not only cell adhesion, but also in inside-out and outside-in signalling. We and others have shown that, in addition to adhesion receptors, podocytes constitutively express functional transmembrane receptor complexes for IL-4, IL-10, IL-13 [152,153] and TNF-α [154]. The IL-4/IL-13 receptor complex is also expressed by endothelial cells, including glomerular epithelium in vivo [152,155]. The presence of cytokine receptors at the glomerular capillary wall is puzzling and raises teleological questions: what is their significance in normal states and what is their role in disease?

In immune cells, cytokines function as soluble messengers and binding of cytokines to their cognate receptors induces a variety of intracellular changes, which have been studied extensively. These changes include cytoskeletal rearrangements, as has been shown for IL-4 and IL-13 in B-cells, granulocytes and macrophages [156–160]. Also, in cultured HUVECs (human umbilical vein endothelial cells), IL-4 and IL-13 regulate cell morphology, cytoskeleton and proliferation [161]. In cultured podocytes, we have shown that IL-4 and IL-13 directly alter protein sorting, ion transport and activity of lysosomal enzymes, such as cathepsin L and heparanase [152,162]. Others have shown the effects of pro-inflammatory cytokines IL-1β and TNF-α on the expression of nephrin by podocytes [163] and on cytoskeleton reorganization in podocytes [164].

Thus cytokine receptors render the glomerular capillary wall responsive to immunological signals from the environment. One may hypothesize that, under physiological circumstances, the levels of circulating cytokines are low and their effects at the glomerular capillary wall may be less pronounced, whereas, in disease, elevated
cytokine levels may induce several changes and eventually lead to an increased glomerular permeability to protein. Alternatively, binding of cytokines to their receptors at the glomerular capillary wall may stimulate the production of other factors by endothelial cells and/or podocytes, which, in turn, may function as permeability factors in a paracrine or autocrine manner.

It is particularly difficult to translate work in vitro to the situation in vivo, since the glomerular capillary filter is a complex structure with multiple interactions that cannot be studied in vitro. The effect of IL-4 on the glomerular capillary wall in vivo was elegantly shown in two successive studies on IL-4 transgenic mice. Transgenic mice that overexpressed IL-4 under the control of an MHC class I promoter developed glomerular FSGS-like lesions associated with proteinuria [165]. This phenotype was associated with increased production of autoantibodies and the presence of immunoglobulin deposits in the glomerular filter, and renal disease could be prevented by treatment with IL-4-neutralizing antibodies. In a cross-breeding experiment with these mice and with &mu;MT -/-, IL-4 transgenic mice were generated that were unable to produce immunoglobulins. In the absence of glomerular deposits, these mice still displayed FSGS-like lesions and proteinuria [166]. It is possible that, in these mice, direct effects of IL-4 on the glomerular capillary wall via the IL-4 receptor were involved in the development of disease. In contrast with IL-4, overexpression of IL-13 in transgenic mice under the control of the CD2 promoter [167] did not induce glomerular abnormalities or proteinuria (J. G. van den Berg, unpublished work).

CONCLUDING REMARKS AND PERSPECTIVES

In summary, idiopathic NS is associated with complex disturbances in the immune system, such as atopy and allergy, and a cytokine bias towards Th2 cytokines. Although these cytokines can act directly on podocytes and the glomerular filtration barrier, the action of a single cytokine may not be sufficient to induce disease. The finding that only few allergic patients develop NS, while they all show high levels of circulating Th2 cytokines, would suggest that one or more additional factors may be required. Rather than being caused by one circulating cytokine, we hypothesize that idiopathic non-familial NS may be a multifactorial disease including intrinsic and environmental factors. The search for complex interrelated mechanisms poses a great challenge, and lessons should be drawn from the recent discoveries in the field of familial NS.

As discussed above briefly, mutations in the gene NPHS2 encoding the podocyte-specific protein podocin are causative of autosomal recessive steroid-resistant NS. Recent studies suggest that even in some NPSH2 patients, circulating factors play a role in addition to the pathogenic mutation [168]. In a subgroup of NPSH2 patients, proteinuria has been reported to recur shortly after renal transplantation in a manner that would exclude the involvement of antibodies [169–171]. In some patients, the disease is partly responsive to treatment with immunosuppressive drugs, which may point to the involvement of the immune system even in this form of NS [172].

Thus, in some patients, both circulating permeability factors and podocyte factors are involved in the development of NS. Antignac [168] proposed that allelic variants or heterozygous mutations in NPHS2 or other podocyte genes may modulate the phenotype of a nephropathy that would arise from the presence of a circulating permeability factor; these podocyte gene variants would act not as causative genes, but as phenotype modifiers. The prevalence of podocin mutations in idiopathic non-familial NS patients is currently under investigation. The first reports show that approx. one quarter of sporadic FSGS is associated with mutations in the podocin gene, whereas no mutations are found in MCNS patients [171]. Other cases of non-familial FSGS have recently been associated with mutations in the gene encoding CD2AP [173]. The search for additional (podocyte) factors involved in the pathogenesis in idiopathic non-familial NS continues. A gene that may encode a yet unknown factor involved in MCNS may be located at chromosome 2p12–p13.2, as has been recently suggested by linkage studies on three siblings with a familial form of MCNS [174].

The involvement of multiple factors, including some intrinsic to podocytes, in the pathogenesis of idiopathic NS does not rule out the possibility of a simple specific therapy. A multifactorial aetiology with involvement of multiple cytokines and chemokines has been established for Th2-associated diseases such as asthma and atopic dermatitis; yet therapeutic strategies aimed at one of the cytokines involved have shown promising results [175–177]. Large prospective multicentre studies that will include genetic linkage analysis are warranted to unravel further which factors are involved in the pathogenesis of idiopathic NS and to develop rational targeted therapies.

ACKNOWLEDGMENTS

We wish to thank Nike Claessen, Sandrine Florquin and Jan Aten for invaluable help and support. This work was supported by grants from the Dutch Kidney Foundation (No. C98.1720), and from The Netherlands Organization for Scientific Research (NWO; Grant 920–903–062).

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Received 26 March 2004/11 May 2004; accepted 25 May 2004
Published as Immediate Publication 25 May 2004, DOI 10.1042/CS20040095