ChiKD CHILDHOOD KIDNEY DISEASES

Review Article

Child Kidney Dis 2023;27(1):1-10
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.22.042

Immunopathogenesis of childhood idiopathic nephrotic syndrome

Hae Il Cheong[1]

[1]Department of Pediatrics, Seoul Red Cross Hospital, Seoul, Republic of Korea

Pediatric nephrotic syndrome (NS) is a clinical syndrome characterized by massive proteinuria, hypoalbuminemia, and generalized edema. Most childhood NS cases are idiopathic (with an unknown etiology). Traditional therapeutic approaches based on immunosuppressive agents largely support the key role of the immune system in idiopathic NS (INS), especially in the steroid-sensitive form. Although most previous studies have suggested the main role of T cell dysfunction and/or the abnormal secretion of certain glomerular permeability factors, recent studies have emphasized the role of B cells since the therapeutic efficacy of B cell depletion therapy in inducing and/or maintaining prolonged remission in patients with INS was confirmed. Furthermore, several studies have detected circulating autoantibodies that target podocyte proteins in a subset of patients with INS, suggesting an autoimmune-mediated etiology of INS. Accordingly, a new therapeutic modality using B cell-depleting drugs has been attempted, with significant effects in a subset of patients with INS. Currently, INS is considered an immune-mediated disorder caused by a complex interplay between T cells, B cells, soluble factors, and podocytes, which may vary among patients. More in-depth investigations of the pathogenic pathways of INS are required for an effective personalized therapeutic approach and to define precise targets for therapeutic intervention.

Keywords: Autoimmunity; B-lymphocytes; Etiology; Nephrotic syndrome

Introduction

Nephrotic syndrome (NS) in children is a clinical syndrome characterized by massive proteinuria, hypoalbuminemia, and generalized edema. Although NS has various etiologies, including genetic mutations, infectious diseases, drugs, and systemic diseases, most cases are idiopathic with an unknown etiology. Idiopathic NS (INS) is the most frequent glomerular disease in the pediatric population, and its prevalence ranges between 1.15 and 16.9 per 100,000 children per year [1]. The two major histological variations of INS in children are minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS); INS can also be classified based on the response to corticosteroid therapy into steroid-sensitive NS (SSNS) and steroid-resistant NS (SRNS).

Massive albuminuria, the hallmark of INS, is caused by damage to podocytes and is histologically characterized by podocyte foot process effacement, loss of podocyte architecture, and loss of slit diaphragm integrity in the absence of inflammatory changes. Therefore, INS is also considered as a major form of podocytopathy [2]. Although the exact pathogenesis of INS has not been fully clarified, traditional therapeutic approaches based on immunosuppressive agents largely support the key role of the immune system, especially in SSNS. Most previous

Received: December 13, 2022; Revised: February 21, 2023; Accepted: February 21, 2023

Correspondence to
Hae Il Cheong
Department of Pediatrics, Seoul Red Cross Hospital, 9 Saemunan-ro, Jongno-gu, Seoul 03181, Republic of Korea
E-mail: cheonghi@snu.ac.kr

studies have suggested that the main pathogenesis of INS is T cell dysfunction and/or abnormal secretion of certain glomerular permeability factors. However, recent studies have suggested that the pathogenesis may also be related to B cell dysfunction.

In this review, an overview of the immunopathogenesis and a detailed review of the emerging autoimmune-mediated etiology of INS are described.

T cells

MCD/INS has been considered a T cell-mediated disorder since 1974, when Shalhoub [3] proposed the hypothesis that MCD is a systemic disorder of T cell dysfunction that results in increased plasma levels of lymphocyte-derived permeability factors. Shalhoub's hypothesis was based on several clinical observations: (1) the lack of evidence of a humoral antibody response (the absence of immune complexes in glomeruli); (2) remission induced by measles, which suppresses cell-mediated immunity; (3) the therapeutic response to steroids and cyclophosphamide, which also suppresses cell-mediated responses, and (4) the occurrence of this syndrome in T cell-derived Hodgkin disease. Additionally, the susceptibility of untreated patients to pneumococcal infections may be of primary or secondary pathogenic importance. Lagrue et al. [4] in 1975 reported the first experimental evidence for the pathophysiological role of lymphocytes in INS by showing that intradermal injection of concanavalin A-stimulated lymphocyte culture supernatants from patients with MCD resulted in the liberation of a soluble lymphokine that increased the permeability of guinea pig skin capillaries.

Thereafter, many observations have indicated that INS is caused by soluble permeability factors in the plasma. In 1984, Zimmerman [5] showed that serum from patients with post-transplant relapse of INS can induce proteinuria in rats. In 1991, Koyama et al. [6] provided strong experimental evidence that supernatants from T-cell hybridomas from patients with MCD can induce proteinuria in rats.

It is well known that idiopathic FSGS rapidly recurs in 40% to 60% of transplant recipients [7], and there have been several lines of evidence indicating a direct or indirect role of circulating glomerular permeability factor in the development of recurrent FSGS: (1) very rapid recurrence within hours after renal transplantation [8]; (2) the efficacy of plasma exchange and selective apheresis methods in treating this condition [9,10]; and (3) resolution of recurrent FSGS after rapid graft re-transplantation from a patient with FSGS recurrence to a diabetic recipient [11]. In addition, transplacental passage of the glomerular permeability factor can induce transient NS in the fetus [12]. These observations have prompted studies to identify circulating permeability factors, focusing on T cell products. Several candidate molecules have been identified, including T-helper 1 (Th1) cytokines (tumor necrosis factor-α [TNF-α], interleukin [IL]-2, and IL-18), T-helper 2 (Th2) cytokines (IL-4 and IL-13), and T-helper 17 (Th17)-related cytokines (IL-17, IL-1β, IL-6, and IL-23) [13,14].

On the other hand, several studies have reported altered numbers or phenotypes of T cell subsets in patients with INS: (1) imbalance between T-helper (CD4+) and T-cytotoxic (CD8+) lymphocytes, with a predominance of CD8+ cells [15,16]; (2) Th1 and Th2 imbalance, with Th2 response predominance [17]; and (3) predominance of Th17 cells, with downregulated T-regulatory cells (Tregs) [18,19]. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome is a rare disease caused by genetic mutations in *FOXP3*, which encodes a transcription factor responsible for the generation and maturation of Tregs. The development of MCD in patients with IPEX syndrome supports the role of Treg dysfunction in INS pathogenesis [20,21].

However, despite these extensive studies, some of the findings have not been consistent across all studies, and there is still no evidence that a specific pathogenic T cell population or product is a key mediator of INS.

Circulating permeability factors

In addition to cytokines, several other circulating permeability factors, including hemopexin, cardiotrophin-like cytokine 1 (CLC-1), soluble urokinase-type plasminogen activator receptor (suPAR), cathepsin L (CatL), angiopoietin-like-4 (Angptl4), apolipoprotein A-I (APOL1), sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b), and calcium/calmodulin-serine protein kinase (CASK), have been shown to increase the permeability of the glomerular filtration barrier. These factors may be involved in INS pathogenesis [22].

Hemopexin

Hemopexin, a protease secreted by the liver, is the first molecule proposed to be a potential permeability factor [23]. Active

https://doi.org/10.3339/ckd.22.042

hemopexin reduces the expression of glomerular sialoglycoproteins and alters the integrity of the actin cytoskeleton in cultured human podocytes [24]; plasma hemopexin activity is increased during recurrence of MCD in pediatric patients [25].

Soluble urokinase-type plasminogen activator receptor (suPAR)

Some studies have shown that the induction of urokinase-type plasminogen activator receptor (uPAR) in podocytes can lead to foot process effacement and proteinuria, and elevated plasma suPAR levels can be a specific diagnostic biomarker for distinguishing SRNS from SSNS and predicting the recurrence of FSGS in the grafted kidney [26-28]. However, several other studies could not confirm the predictive value of suPAR in distinguishing FSGS from other glomerular pathologies such as MCD, membranous nephropathy, IgA nephropathy, lupus nephritis, or non-glomerular chronic kidney disease [29,30], and suPAR injection alone does not induce proteinuria in wild-type mice [31]. Furthermore, plasma suPAR levels are influenced by renal function and are elevated in other kidney and liver diseases [32].

Cardiotrophin-like cytokine 1 (CLC-1)

Savin et al. [33,34] proposed that CLC-1, a member of the IL-6 cytokine family, is a pathogenic circulating factor in FSGS. CLC-1 was first identified in plasma samples of patients with post-transplant recurrence of FSGS [34]. Recombinant monomeric human CLC-1 induces albuminuria in mice and increases albumin permeability in isolated rat glomeruli [34]. Clinically, CLC-1 was increased in patients with recurrent FSGS, and proteinuria decreased significantly after the administration of CLC-1 antibodies [34].

Angiopoietin-like-4 (Angptl4)

Angptl4 is a glycoprotein that is strongly expressed in adipose tissue and the liver. Angptl4 has been suggested to play a role in the development of proteinuria in MCD [35,36]. Overexpression of Angptl4 in podocytes has been reported in relapsed MCD in experimental animal models, including a puromycin aminonucleoside nephrosis model [35]. However, a large-sample study reported that Angptl4 was not expressed in the glomeruli of patients with MCD in relapse [36].

Podocytes

In 2004, Reiser et al. [37] reported an interesting observation that lipopolysaccharide injection led to NS in both wild-type and severe combined immunodeficient mice, suggesting that this mouse model of MCD may develop without the involvement of T or B cells. On the other hand, podocytes have attracted attention as a novel key player in the immunopathogenesis of INS [22,38,39].

CD80, also known as B7-1, is expressed in activated B cells and antigen-presenting cells and plays an important role in B-cell and T-cell interactions. Activation of CD80 on antigen-presenting cells and binding to the CD28 receptor on T-cells play key roles in T-cell activation, while binding of CD80 to cytotoxic T-lymphocyte-associated-4 (CTLA-4) terminates the T-cell response [40]. Podocytes express CD80 and can, therefore, act as antigen-presenting immune cells [37,41,42]. In 2004, Reiser et al. [37] found podocyte CD80 expression in various clinical and experimental kidney diseases with NS, and its expression was correlated with the severity of human lupus nephritis. Shimada et al. [39], in 2011, proposed that MCD is a "two-hit" podocyte immune disorder based on experimental studies [40,42]. The "first hit" is induction of podocyte expression of CD80 in response to a circulating factor (such as a cytokine, allergen, or microbial product). Increased podocyte CD80 expression results in transient proteinuria due to autoregulatory mechanisms mediated by T cells and/or podocytes. The "second hit" is dysfunction of this autoregulatory mechanism, resulting in persistent CD80 expression and proteinuria. CD80 expression is inhibited by both CTLA-4 and IL-10, resulting in the resolution of proteinuria [43,44]. If dysfunctional Tregs in patients with MCD cannot turn off podocyte CD80 expression by secretion of soluble CTLA-4, IL-10, and transforming growth factor-beta, proteinuria may persist.

Several subsequent studies revealed that the concentration of soluble CD80 and the ratio of CD80/CTLA-4 in urine were significantly higher in patients with relapsing MCD than in those in remission, which is a characteristic of MCD versus FSGS [45-47]. Therefore, CD80 has been proposed as a potential differentiating biomarker of MCD histology and responsiveness to steroids and immunosuppressive treatments [48,49].

Abatacept (CTLA4–Ig) is a fusion protein composed of the Fc region of the immunoglobulin G1 (IgG1) fused to the extracellular domain of CTLA-4. Abatacept blocks the CD80–CD28 pathway by competing with CD28 in binding to CD80, thereby

inducing apoptosis and T cell incompetence. The alleviation of proteinuria in some patients with rituximab- and steroid-resistant FSGS after abatacept supplementation also indicates the role of CD80 in the pathogenesis of FSGS [50,51]. At the moment, the exact role of CD80/CTLA-4 in the pathogenesis of INS and the effect of abatacept in refractory NS has not been confirmed and has been criticized in several papers that reported different results [50,52-55].

Podocytes also express human leukocyte antigen (HLA) class II like immune cells [41]. Aberrant HLA class II expression causes autoimmune diseases affecting antigen-presenting cells and various organs [56]. These findings also suggest that podocytes act as immune cells in the pathogenesis of NS.

B cells

In 2004, sustained remission of NS in a boy treated with rituximab, a B cell-depleting anti-CD20 monoclonal antibody, for recurrent idiopathic thrombocytopenic purpura was observed by chance [57]. Several subsequent studies have demonstrated the therapeutic efficacy of B cell-depleting therapy in inducing and/or maintaining prolonged remission in both pediatric and adult patients with INS [58,59]. These findings support a key role for B cells in INS pathogenesis. In addition, previous findings that INS may occur in association with non-Hodgkin lymphoproliferative disorders (such as B cell-derived Hodgkin lymphoma) and Epstein-Barr virus infection provided additional evidence for the role of B cells [60,61]. Interestingly, mycophenolate mofetil and calcineurin inhibitors, known to target T cells, are also effective in inhibiting B cell proliferation and immunoglobulin production and can contribute to maintaining remission following anti-CD20 treatment [62,63]. Recently, ofatumumab, a humanized anti-CD20 monoclonal antibody, has been shown to be beneficial in some patients with rituximab-resistant INS [64]. In addition, global anti-B cell targeting with a combination of obinutuzumab (a humanized anti-CD20 monoclonal antibody) and daratumumab (a recombinant anti-CD38 monoclonal antibody targeting plasma cells) demonstrated promising results in rituximab-resistant pediatric patients with NS [65].

B cells can play a role in the pathogenesis of INS by producing pathogenic antibodies against podocyte proteins (see "autoantibodies" section below) and by antibody-independent mechanisms. B cells can also secrete various cytokines including IL-13, TNF-α, IL-4, interferon-γ, IL-6, and IL-17 [66]. IL-13 and IL-4 are related to atopy, a condition that can trigger the first or recurrent episodes of NS [67].

An increased amount of serum CD23, a marker of B-cell activation, has been reported in pediatric SSNS [68], and concomitantly increased levels of soluble CD25 (a T-cell activation marker) and soluble CD23 were also observed in pediatric patients with SSNS in relapse [69]. These findings suggest a potential role for B cells in sustaining T-cell stimulation. Increased levels of serum B-cell activating factor and IL-21, which contribute to B-cell activation, have been observed in adult patients with MCD [70]. In an experimental mouse model, IL-4 secreting B cells activated locally in glomeruli could induce proteinuria and foot process effacement [71]. Recently, several large transethnic genome-wide association studies in large pediatric cohorts, including Korean patients, revealed specific risk alleles in the HLA region that play a crucial role in antigen presentation to T cells [72-74]. Alterations in B cell phenotypes, such as increased circulating levels of total B cells and memory B cells, have also been observed during the active phase of the disease in children with SSNS [63,75,76].

These findings suggest that memory B cells play a key role in the pathogenesis of pediatric SSNS, and that the reappearance of memory B cells can predict relapse following B cell depletion therapy in childhood SSNS [63,77].

Autoimmunity

INS has traditionally not been considered an antibody-mediated or autoimmune disease because of the lack of immune complex deposits in kidney biopsy specimen. However, Dantal et al. [78], in 1998, suggested a pathogenic role for circulating antibodies in INS by showing that a permeability factor inducing proteinuria could be an immunoglobulin or be bound to an immunoglobulin. Thereafter, several studies have been conducted to detect pathogenic circulating autoantibodies in patients with INS; findings of these studies include IgM antibodies targeting the actin cytoskeleton type in a subset of patients with INS with FSGS/mesangial IgM glomerulonephritis [79] and autoantibodies against angiotensin 2 receptor in a transplant patient with FSGS [80]. In a study among patients with FSGS who underwent kidney transplantation, Delville et al. [31] found that increased levels of circulating anti-CD40 IgG predicted disease recurrence in grafted kidneys, and they detected CD40 expression in podocytes of the affected kidneys. These antibodies disrupted the actin cytoskeleton of cultured podocytes and induced proteinuria (in the presence of recombinant soluble

https://doi.org/10.3339/ckd.22.042

urokinase plasminogen activator receptor) in injected mice. A CD40 blocking antibody reversed these effects.

Recently, more systematic studies have detected circulating IgG autoantibodies that target several podocyte proteins in a subset of patients with INS (Table 1). In 2018, a French group suggested the causative role of autoantibodies against podocyte ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) in the development of INS [81]. Plasma samples were obtained from 85 children with steroid-sensitive INS during relapse or remission. After plasma fractionation by size exclusion chromatography, detachment of cultured podocytes was observed, with one IgG-containing fraction from 47% (16 of 34) of patients in relapse, 9% of patients in remission, and 0% of controls. Total podocyte protein lysates were immunoprecipitated by IgG from the plasma fractions, thereby identifying an array of podocyte proteins. Subsequent proteomic analyses identified UCHL1 as the target podocyte protein, and anti-UCHL1 IgG led to podocyte detachment. The degree of proteinuria correlated with the circulating anti-UCHL1 IgG levels at various stages of the disease; the plasma levels were significantly higher in patients with relapsing INS than in patients in remission and controls. Purified patient anti-UCHL1 antibodies induced proteinuria and podocyte foot effacement in mice. These findings support the causative role of anti-UCHL1 autoantibodies in INS development. They also found cell surface expression of UCHL1 on podocytes and the presence of urinary anti-UCHL1 antibodies in the patients. These findings support the hypothesis that *in situ* formation of surface UCHL1-anti-UCHL1 IgG autoantibody complexes results in podocyte detachment and, subsequently, the absence of IgG deposits on kidney biopsies in INS. UCHL1, a deubiquitinating enzyme, is expressed by podocytes and plays a major role in maintaining foot process formation [82]. UCHL1 is overexpressed in the podocytes of patients with various types of glomerulopathies with massive proteinuria, including primary membranous nephropathy, genetic NS, lupus nephritis, and IgA nephropathy, but it is downregulated in MCD [83,84].

In 2021, a Chinese group reported that circulating annexin A2 autoantibodies may be responsible for some cases of childhood INS with MCD/FSGS [85]. They first recruited 20 children with initial onset of INS before immunosuppressive treatment, and the presence of specific IgG-type autoantibodies against podocytes in the sera was verified via mouse podocyte immunofluorescence in 14 of the 20 children. Western blotting and mass spectrometry analysis confirmed that annexin A2 was the target antigen of the IgG-type autoantibody. They then screened 596 children with INS without genetic mutations and found that 106 (17.8%) of them had circulating annexin A2 autoantibody in their sera. Autoantibodies were not detected in children with other glomerular diseases, such as Henoch–Schonlein nephritis, IgA nephropathy, isolated proteinuria, and lupus nephritis, or in healthy controls. Renal biopsy was performed for 61 of the 106 children (including 33 children with SRNS and 28 with frequent relapsing NS/steroid dependent NS), which revealed MCD or FSGS in all cases. Remission of NS by immunosuppressant therapy was accompanied by decreased levels of anti-annexin A2 antibodies in all 30 children observed. They also found that IgG4 subtype anti-annexin A2 antibodies, co-localized with nephrin, was present on the surface of glomerular podocytes in kidney biopsy tissue. Intravenous injection of a commercial anti-annexin A2 antibody induced podocyte injury and proteinuria in BALB/c mice, and addition of anti-annexin A2 antibody to podocyte culture media reduced adhesion, migration, and phagocytic abilities and destroyed the F-actin structure of podocytes. Annexin A2 antibody has been reported in patients with lupus nephritis [88], Behçet disease [89], and anti-phospholipid antibodies [90]. Annexin A2 is known to play an important role in cytoskeletal rearrangement and various membrane-related changes in podocytes [91], and this study suggests that autoantibodies against annexin A2 could affect the rearrangement of podocyte cytoskeleton proteins by re-

Table 1. Studies detecting circulating immunoglobulin G autoantibodies targeting podocyte proteins in patients with idiopathic nephrotic syndrome

Study	Age and disease of subjects	Target protein	Detection rate, n/n (%)
Jamin et al. [81]	Children with SS-INS	UCHL1	16/34 (47)
Ye et al. [85]	Children with INS of nongenetic origin	Annexin A2	106[a]/596 (18)
Ye et al. [86]	Children with INS	Vinculin and 6 more antigens	199/341 (66)
Watts et al. [87]	Children and adults with biopsy-proven MCD	Nephrin	18/62 (29)

SS-INS, steroid-sensitive idiopathic nephrotic syndrome; UCHL1, ubiquitin carboxy-terminal hydrolase L1; INS, idiopathic nephrotic syndrome; MCD, minimal change disease.
[a]33 Children with steroid-resistant nephrotic syndrome.

acting with annexin A2, thereby causing damage to podocyte functions and eventually inducing proteinuria.

In the same year, the same Chinese group published a subsequent comprehensive paper on the podocyte autoantibody spectrum in the sera of patients with INS using two-dimensional electrophoresis and mass spectrometry [86]. They detected seven types of podocyte autoantibodies that were most related to the onset of NS in the sera of 66% of children with INS, of whom 24% were positive for a single autoantibody and 42% were positive for multiple autoantibodies in various combinations. The most common were autoantibodies against vinculin, followed by serine arginine-rich splitting factor 9, proteasome subunit alpha type 1, aconitate hydratase 2, peptidyl prolyl cis-trans isomerase D, peroxiredoxin, and F-actin capping protein subunit beta. The level of podocyte autoantibodies above the threshold was positively correlated with the 24-hour urinary protein content in the patients, and the antibody level was reduced below the threshold with proteinuria remission. Based on the results of both studies, the authors suggested a novel subgroup of childhood INS with a high level of podocyte autoantibodies in their sera—autoimmune podocytopathies [86,92]. They also suggested that the absence of immune complex deposits in the glomeruli of this subgroup of patients does not preclude the etiology and diagnosis of autoantibody-mediated renal disease, as in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis.

Nephrin is an essential structural and functional component of the slit diaphragm, and genetic mutations in the *NPHS1* gene, which encodes nephrin, cause Finnish type congenital NS [93]. In animal models, injection of antibodies targeting nephrin induces massive proteinuria [94,95]. In addition, alloantibodies against nephrin and complete nephrin deficiency may develop following kidney transplantation in children with Finnish type congenital NS, causing recurrence of proteinuria in the grafted kidney [96,97]. In 2022, a Boston group presented further evidence of the autoimmune etiology of INS by detecting circulating autoantibodies against nephrin in a subset of patients with MCD [87]. They evaluated sera obtained from the Nephrotic Syndrome Study Network longitudinal cohort study [98] consisting of 41 (66%) children and 21 (34%) adults using an indirect enzyme-linked immunosorbent assay, and found that 18 (29%) of the 62 patients, with an equal number of adults and children, had circulating autoantibodies against nephrin in their sera obtained during the active disease state. During complete or partial remission of proteinuria, circulating nephrin autoantibodies were completely absent or significantly reduced, respectively. They also found that podocyte-associated punctate IgG staining, which specifically co-localized with nephrin, was present in a subset of MCD kidney biopsies, and circulating autoantibodies against nephrin were exclusively present in patients with renal biopsy IgG-positive MCD. They observed two predominant patterns of IgG distribution: glomerular basement membrane–associated fine punctate or curvilinear structures and more apically located punctate and vaguely vesicular clusters, with the latter being more common. These disparate staining patterns may reflect the different stages of antibody binding and/or redistribution. They also encountered a girl with steroid-dependent childhood MCD that progressed to end-stage kidney disease; she developed post-transplant recurrence of massive proteinuria in association with high pre-transplant circulating autoantibodies against nephrin.

In 2022, Hada et al. [99] developed a novel mouse model of massive proteinuria via active immunization with the recombinant extracellular domain of murine crumb cell polarity complex component 2 (Crb2), an essential slit diaphragm protein of the glomerular filtration barrier [100]. Active immunization of mice with either a single injection or three injections of recombinant Crb2 resulted in the development of circulating anti-Crb2 autoantibodies and significant albuminuria 4 weeks after the first immunization. The albuminuria persisted for up to 29 weeks. The initial kidney pathology findings were similar to that of MCD in humans, and interestingly, immunofluorescence microscopic findings revealed delicate punctate IgG staining in the glomeruli, which co-localized with Crb2 in podocyte foot processes. A subset of mice that were administered three injections also developed hematuria, a higher level of proteinuria, and histologic features of FSGS after 18 weeks. Therefore, NS induced in this mouse model mimics the clinical and pathological features of human MCD and FSGS when the injury is more severe. Although specific autoantibodies against Crb2 have not yet been identified in patients with INS, this is the first autoimmune-mediated mouse model of MCD and possibly FSGS, and this model will be very useful in elucidating the autoimmune pathogenesis of INS.

Conclusion

Although the pathogenesis of INS is not completely understood, it seems likely that INS is an immune-mediated disorder caused by a complex interplay between immunoregulatory

https://doi.org/10.3339/ckd.22.042

cells, soluble factors, and podocytes, which may vary between patients. Recently, a growing body of evidence has suggested a key role of B cells in the pathogenesis of INS, and accordingly, a new therapeutic modality using B cell-depleting drugs has been attempted with significant effects, at least in a subset of patients with INS. A more in-depth investigation of the pathogenic pathways of INS is required to define precise targets for therapeutic intervention and to lead to a more effective personalized therapeutic approach.

Conflicts of interest

Hae Il Cheong is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

All the work was done by HIC.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet 2018;392:61-74.
2. Barisoni L, Schnaper HW, Kopp JB. A proposed taxonomy for the podocytopathies: a reassessment of the primary nephrotic diseases. Clin J Am Soc Nephrol 2007;2:529-42.
3. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. Lancet 1974;2:556-60.
4. Lagrue G, Xheneumont S, Branellec A, Hirbec G, Weil B. A vascular permeability factor elaborated from lymphocytes. I. Demonstration in patients with nephrotic syndrome. Biomedicine 1975;23:37-40.
5. Zimmerman SW. Increased urinary protein excretion in the rat produced by serum from a patient with recurrent focal glomerular sclerosis after renal transplantation. Clin Nephrol 1984;22:32-8.
6. Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M. A glomerular permeability factor produced by human T cell hybridomas. Kidney Int 1991;40:453-60.
7. Kienzl-Wagner K, Waldegger S, Schneeberger S. Disease recurrence: the sword of Damocles in kidney transplantation for primary focal segmental glomerulosclerosis. Front Immunol 2019;10:1669.
8. Hoyer JR, Vernier RL, Najarian JS, Raij L, Simmons RL, Michael AF. Recurrence of idiopathic nephrotic syndrome after renal transplantation. Lancet 1972;2:343-8.
9. Laufer J, Ettenger RB, Ho WG, Cohen AH, Marik JL, Fine RN. Plasma exchange for recurrent nephrotic syndrome following renal transplantation. Transplantation 1988;46:540-2.
10. Dantal J, Bigot E, Bogers W, Testa A, Kriaa F, Jacques Y, et al. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. N Engl J Med 1994;330:7-14.
11. Gallon L, Leventhal J, Skaro A, Kanwar Y, Alvarado A. Resolution of recurrent focal segmental glomerulosclerosis after retransplantation. N Engl J Med 2012;366:1648-9.
12. Kemper MJ, Wolf G, Muller-Wiefel DE. Transmission of glomerular permeability factor from a mother to her child. N Engl J Med 2001;344:386-7.
13. Kitsou K, Askiti V, Mitsioni A, Spoulou V. The immunopathogenesis of idiopathic nephrotic syndrome: a narrative review of the literature. Eur J Pediatr 2022;181:1395-404.
14. Campbell RE, Thurman JM. The immune system and idiopathic nephrotic syndrome. Clin J Am Soc Nephrol 2022;17:1823-34.
15. Kemper MJ, Zepf K, Klaassen I, Link A, Muller-Wiefel DE. Changes of lymphocyte populations in pediatric steroid-sensitive nephrotic syndrome are more pronounced in remission than in relapse. Am J Nephrol 2005;25:132-7.
16. Baris HE, Baris S, Karakoc-Aydiner E, Gokce I, Yildiz N, Cicekkoku D, et al. The effect of systemic corticosteroids on the innate and adaptive immune system in children with steroid responsive nephrotic syndrome. Eur J Pediatr 2016;175:685-93.
17. Bhatia D, Sinha A, Hari P, Sopory S, Saini S, Puraswani M, et al. Rituximab modulates T- and B-lymphocyte subsets and urinary CD80 excretion in patients with steroid-dependent nephrotic syndrome. Pediatr Res 2018;84:520-6.
18. Liu LL, Qin Y, Cai JF, Wang HY, Tao JL, Li H, et al. Th17/Treg imbalance in adult patients with minimal change nephrotic syndrome. Clin Immunol 2011;139:314-20.
19. Stachowski J, Barth C, Michalkiewicz J, Krynicki T, Jarmolinski T, Runowski D, et al. Th1/Th2 balance and CD45-positive T cell subsets in primary nephrotic syndrome. Pediatr Nephrol 2000;14:779-85.
20. Park E, Chang HJ, Shin JI, Lim BJ, Jeong HJ, Lee KB, et al. Familial IPEX syndrome: different glomerulopathy in two siblings. Pediatr Int 2015;57:e59-61.
21. Hashimura Y, Nozu K, Kanegane H, Miyawaki T, Hayakawa A, Yoshikawa N, et al. Minimal change nephrotic syndrome associated with

immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. Pediatr Nephrol 2009;24:1181-6.
22. Chen J, Qiao XH, Mao JH. Immunopathogenesis of idiopathic nephrotic syndrome in children: two sides of the coin. World J Pediatr 2021;17:115-22.
23. Cheung PK, Stulp B, Immenschuh S, Borghuis T, Baller JF, Bakker WW. Is 100KF an isoform of hemopexin? Immunochemical characterization of the vasoactive plasma factor 100KF. J Am Soc Nephrol 1999;10:1700-8.
24. Lennon R, Singh A, Welsh GI, Coward RJ, Satchell S, Ni L, et al. Hemopexin induces nephrin-dependent reorganization of the actin cytoskeleton in podocytes. J Am Soc Nephrol 2008;19:2140-9.
25. Bakker WW, van Dael CM, Pierik LJ, van Wijk JA, Nauta J, Borghuis T, et al. Altered activity of plasma hemopexin in patients with minimal change disease in relapse. Pediatr Nephrol 2005;20:1410-5.
26. Wei C, Moller CC, Altintas MM, Li J, Schwarz K, Zacchigna S, et al. Modification of kidney barrier function by the urokinase receptor. Nat Med 2008;14:55-63.
27. Wei C, El Hindi S, Li J, Fornoni A, Goes N, Sageshima J, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat Med 2011;17:952-60.
28. Peng Z, Mao J, Chen X, Cai F, Gu W, Fu H, et al. Serum suPAR levels help differentiate steroid resistance from steroid-sensitive nephrotic syndrome in children. Pediatr Nephrol 2015;30:301-7.
29. Meijers B, Maas RJ, Sprangers B, Claes K, Poesen R, Bammens B, et al. The soluble urokinase receptor is not a clinical marker for focal segmental glomerulosclerosis. Kidney Int 2014;85:636-40.
30. Sinha A, Bajpai J, Saini S, Bhatia D, Gupta A, Puraswani M, et al. Serum-soluble urokinase receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children. Kidney Int 2014;85:649-58.
31. Delville M, Sigdel TK, Wei C, Li J, Hsieh SC, Fornoni A, et al. A circulating antibody panel for pretransplant prediction of FSGS recurrence after kidney transplantation. Sci Transl Med 2014;6:256ra136.
32. Konigshausen E, Sellin L. Circulating permeability factors in primary focal segmental glomerulosclerosis: a review of proposed candidates. Biomed Res Int 2016;2016:3765608.
33. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2010;5:2115-21.
34. Savin VJ, Sharma M, Zhou J, Gennochi D, Fields T, Sharma R, et al. Renal and hematological effects of CLCF-1, a B-cell-stimulating cytokine of the IL-6 family. J Immunol Res 2015;2015:714964.
35. Clement LC, Avila-Casado C, Mace C, Soria E, Bakker WW, Kersten S, et al. Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome. Nat Med 2011;17:117-22.
36. Cara-Fuentes G, Segarra A, Silva-Sanchez C, Wang H, Lanaspa MA, Johnson RJ, et al. Angiopoietin-like-4 and minimal change disease. PLoS One 2017;12:e0176198.
37. Reiser J, von Gersdorff G, Loos M, Oh J, Asanuma K, Giardino L, et al. Induction of B7-1 in podocytes is associated with nephrotic syndrome. J Clin Invest 2004;113:1390-7.
38. Chugh SS, Clement LC, Mace C. New insights into human minimal change disease: lessons from animal models. Am J Kidney Dis 2012;59:284-92.
39. Shimada M, Araya C, Rivard C, Ishimoto T, Johnson RJ, Garin EH. Minimal change disease: a "two-hit" podocyte immune disorder? Pediatr Nephrol 2011;26:645-9.
40. Alegre ML, Frauwirth KA, Thompson CB. T-cell regulation by CD28 and CTLA-4. Nat Rev Immunol 2001;1:220-8.
41. Goldwich A, Burkard M, Olke M, Daniel C, Amann K, Hugo C, et al. Podocytes are nonhematopoietic professional antigen-presenting cells. J Am Soc Nephrol 2013;24:906-16.
42. Reiser J, Mundel P. Danger signaling by glomerular podocytes defines a novel function of inducible B7-1 in the pathogenesis of nephrotic syndrome. J Am Soc Nephrol 2004;15:2246-8.
43. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, et al. CTLA-4 control over Foxp3+ regulatory T cell function. Science 2008;322:271-5.
44. Mosser DM, Zhang X. Interleukin-10: new perspectives on an old cytokine. Immunol Rev 2008;226:205-18.
45. Cara-Fuentes G, Wasserfall CH, Wang H, Johnson RJ, Garin EH. Minimal change disease: a dysregulation of the podocyte CD80-CTLA-4 axis? Pediatr Nephrol 2014;29:2333-40.
46. Garin EH, Diaz LN, Mu W, Wasserfall C, Araya C, Segal M, et al. Urinary CD80 excretion increases in idiopathic minimal-change disease. J Am Soc Nephrol 2009;20:260-6.
47. Garin EH, Mu W, Arthur JM, Rivard CJ, Araya CE, Shimada M, et al. Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis. Kidney Int 2010;78:296-302.
48. Ling C, Liu X, Shen Y, Chen Z, Fan J, Jiang Y, et al. Urinary CD80 levels as a diagnostic biomarker of minimal change disease. Pediatr Nephrol 2015;30:309-16.
49. Ling C, Liu X, Shen Y, Chen Z, Fan J, Jiang Y, et al. Urinary CD80 excretion is a predictor of good outcome in children with primary nephrotic syndrome. Pediatr Nephrol 2018;33:1183-7.
50. Yu CC, Fornoni A, Weins A, Hakroush S, Maiguel D, Sageshima J, et al. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med 2013;369:2416-23.

https://doi.org/10.3339/ckd.22.042

51. Dado D, Parikh S, Ayoub I, Rovin B, Nadasdy T, Hebert L. Abatacept efficacy in steroid-resistant minimal-change disease revealed by the speed of proteinuria reduction after the start of abatacept. Clin Nephrol 2018;89:376-80.
52. Minamikawa S, Nozu K, Maeta S, Yamamura T, Nakanishi K, Fujimura J, et al. The utility of urinary CD80 as a diagnostic marker in patients with renal diseases. Sci Rep 2018;8:17322.
53. Gonzalez Guerrico AM, Lieske J, Klee G, Kumar S, Lopez-Baez V, Wright AM, et al. Urinary CD80 discriminates among glomerular disease types and reflects disease activity. Kidney Int Rep 2020;5:2021-31.
54. Benigni A, Gagliardini E, Remuzzi G. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med 2014;370:1261-3.
55. Alachkar N, Carter-Monroe N, Reiser J. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med 2014;370:1263-4.
56. Arase N, Arase H. Cellular misfolded proteins rescued from degradation by MHC class II molecules are possible targets for autoimmune diseases. J Biochem 2015;158:367-72.
57. Benz K, Dotsch J, Rascher W, Stachel D. Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy. Pediatr Nephrol 2004;19:794-7.
58. Iijima K, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014;384:1273-81.
59. Gauckler P, Shin JI, Alberici F, Audard V, Bruchfeld A, Busch M, et al. Rituximab in adult minimal change disease and focal segmental glomerulosclerosis: what is known and what is still unknown? Autoimmun Rev 2020;19:102671.
60. Audard V, Larousserie F, Grimbert P, Abtahi M, Sotto JJ, Delmer A, et al. Minimal change nephrotic syndrome and classical Hodgkin's lymphoma: report of 21 cases and review of the literature. Kidney Int 2006;69:2251-60.
61. Kofman T, Zhang SY, Copie-Bergman C, Moktefi A, Raimbourg Q, Francois H, et al. Minimal change nephrotic syndrome associated with non-Hodgkin lymphoid disorders: a retrospective study of 18 cases. Medicine (Baltimore) 2014;93:350-8.
62. Chan EY, Webb H, Yu E, Ghiggeri GM, Kemper MJ, Ma AL, et al. Both the rituximab dose and maintenance immunosuppression in steroid-dependent/frequently-relapsing nephrotic syndrome have important effects on outcomes. Kidney Int 2020;97:393-401.
63. Colucci M, Oniszczuk J, Vivarelli M, Audard V. B-cell dysregulation in idiopathic nephrotic syndrome: what we know and what we need to discover. Front Immunol 2022;13:823204.
64. Wang CS, Liverman RS, Garro R, George RP, Glumova A, Karp A, et al. Ofatumumab for the treatment of childhood nephrotic syndrome. Pediatr Nephrol 2017;32:835-41.
65. Dossier C, Prim B, Moreau C, Kwon T, Maisin A, Nathanson S, et al. A global antiB cell strategy combining obinutuzumab and daratumumab in severe pediatric nephrotic syndrome. Pediatr Nephrol 2021;36:1175-82.
66. Shen P, Fillatreau S. Antibody-independent functions of B cells: a focus on cytokines. Nat Rev Immunol 2015;15:441-51.
67. Abdel-Hafez M, Shimada M, Lee PY, Johnson RJ, Garin EH. Idiopathic nephrotic syndrome and atopy: is there a common link? Am J Kidney Dis 2009;54:945-53.
68. Cho BS, Yoon SR, Jang JY, Pyun KH, Lee CE. Up-regulation of interleukin-4 and CD23/FcepsilonRII in minimal change nephrotic syndrome. Pediatr Nephrol 1999;13:199-204.
69. Kemper MJ, Meyer-Jark T, Lilova M, Muller-Wiefel DE. Combined T- and B-cell activation in childhood steroid-sensitive nephrotic syndrome. Clin Nephrol 2003;60:242-7.
70. Oniszczuk J, Beldi-Ferchiou A, Audureau E, Azzaoui I, Molinier-Frenkel V, Frontera V, et al. Circulating plasmablasts and high level of BAFF are hallmarks of minimal change nephrotic syndrome in adults. Nephrol Dial Transplant 2021;36:609-17.
71. Kim AH, Chung JJ, Akilesh S, Koziell A, Jain S, Hodgin JB, et al. B cell-derived IL-4 acts on podocytes to induce proteinuria and foot process effacement. JCI Insight 2017;2:e81836.
72. Gbadegesin RA, Adeyemo A, Webb NJ, Greenbaum LA, Abeyagunawardena A, Thalgahagoda S, et al. HLA-DQA1 and PLCG2 are candidate risk loci for childhood-onset steroid-sensitive nephrotic syndrome. J Am Soc Nephrol 2015;26:1701-10.
73. Debiec H, Dossier C, Letouze E, Gillies CE, Vivarelli M, Putler RK, et al. Transethnic, genome-wide analysis reveals immune-related risk alleles and phenotypic correlates in pediatric steroid-sensitive nephrotic syndrome. J Am Soc Nephrol 2018;29:2000-13.
74. Jia X, Yamamura T, Gbadegesin R, McNulty MT, Song K, Nagano C, et al. Common risk variants in NPHS1 and TNFSF15 are associated with childhood steroid-sensitive nephrotic syndrome. Kidney Int 2020;98:1308-22.
75. Ling C, Wang X, Chen Z, Fan J, Meng Q, Zhou N, et al. Altered B-lymphocyte homeostasis in idiopathic nephrotic syndrome. Front Pediatr 2019;7:377.
76. Ling C, Chen Z, Fan J, Sun Q, Wang X, Hua L, et al. Decreased circulating transitional B-cell to memory B-cell ratio is a risk factor for relapse in children with steroid-sensitive nephrotic syndrome. Nephron 2021;145:107-12.
77. Colucci M, Carsetti R, Cascioli S, Casiraghi F, Perna A, Rava L, et al. B

cell reconstitution after rituximab treatment in idiopathic nephrotic syndrome. J Am Soc Nephrol 2016;27:1811-22.
78. Dantal J, Godfrin Y, Koll R, Perretto S, Naulet J, Bouhours JF, et al. Antihuman immunoglobulin affinity immunoadsorption strongly decreases proteinuria in patients with relapsing nephrotic syndrome. J Am Soc Nephrol 1998;9:1709-15.
79. Musante L, Candiano G, Bruschi M, Santucci L, Carnemolla B, Orecchia P, et al. Circulating anti-actin and anti-ATP synthase antibodies identify a sub-set of patients with idiopathic nephrotic syndrome. Clin Exp Immunol 2005;141:491-9.
80. Alachkar N, Gupta G, Montgomery RA. Angiotensin antibodies and focal segmental glomerulosclerosis. N Engl J Med 2013;368:971-3.
81. Jamin A, Berthelot L, Couderc A, Chemouny JM, Boedec E, Dehoux L, et al. Autoantibodies against podocytic UCHL1 are associated with idiopathic nephrotic syndrome relapses and induce proteinuria in mice. J Autoimmun 2018;89:149-61.
82. Sun Y, Zhang H, Hu R, Sun J, Mao X, Zhao Z, et al. The expression and significance of neuronal iconic proteins in podocytes. PLoS One 2014;9:e93999.
83. Meyer-Schwesinger C, Meyer TN, Munster S, Klug P, Saleem M, Helmchen U, et al. A new role for the neuronal ubiquitin C-terminal hydrolase-L1 (UCH-L1) in podocyte process formation and podocyte injury in human glomerulopathies. J Pathol 2009;217:452-64.
84. Liu Y, Wu J, Wu H, Wang T, Gan H, Zhang X, et al. UCH-L1 expression of podocytes in diseased glomeruli and in vitro. J Pathol 2009;217:642-53.
85. Ye Q, Zhang Y, Zhuang J, Bi Y, Xu H, Shen Q, et al. The important roles and molecular mechanisms of annexin A2 autoantibody in children with nephrotic syndrome. Ann Transl Med 2021;9:1452.
86. Ye Q, Zhou C, Wang D, Fu H, Wang J, Mao J. Seven novel podocyte autoantibodies were identified to diagnosis a new disease subgroup-autoimmune podocytopathies. Clin Immunol 2021;232:108869.
87. Watts AJ, Keller KH, Lerner G, Rosales I, Collins AB, Sekulic M, et al. Discovery of autoantibodies targeting nephrin in minimal change disease supports a novel autoimmune etiology. J Am Soc Nephrol 2022;33:238-52.
88. Caster DJ, Korte EA, Merchant ML, Klein JB, Wilkey DW, Rovin BH, et al. Autoantibodies targeting glomerular annexin A2 identify patients with proliferative lupus nephritis. Proteomics Clin Appl 2015;9:1012-20.
89. Chen P, Yan H, Tian Y, Xun Y, Shi L, Bao R, et al. Annexin A2 as a target endothelial cell membrane autoantigen in Behçet's disease. Sci Rep 2015;5:8162.
90. Salle V, Maziere JC, Brule A, Schmidt J, Smail A, Duhaut P, et al. Antibodies against the N-terminal domain of annexin A2 in antiphospholipid syndrome. Eur J Intern Med 2012;23:665-8.
91. Hayes MJ, Shao D, Bailly M, Moss SE. Regulation of actin dynamics by annexin 2. EMBO J 2006;25:1816-26.
92. Ye Q, Chen A, Lai EY, Mao J. Autoimmune podocytopathies: a novel sub-group of diseases from childhood idiopathic nephrotic syndrome. J Am Soc Nephrol 2022;33:653-4.
93. Kestila M, Lenkkeri U, Mannikko M, Lamerdin J, McCready P, Putaala H, et al. Positionally cloned gene for a novel glomerular protein--nephrin--is mutated in congenital nephrotic syndrome. Mol Cell 1998;1:575-82.
94. Orikasa M, Matsui K, Oite T, Shimizu F. Massive proteinuria induced in rats by a single intravenous injection of a monoclonal antibody. J Immunol 1988;141:807-14.
95. Takeuchi K, Naito S, Kawashima N, Ishigaki N, Sano T, Kamata K, et al. New anti-nephrin antibody mediated podocyte injury model using a C57BL/6 mouse strain. Nephron 2018;138:71-87.
96. Holmberg C, Jalanko H. Congenital nephrotic syndrome and recurrence of proteinuria after renal transplantation. Pediatr Nephrol 2014;29:2309-17.
97. Kuusniemi AM, Qvist E, Sun Y, Patrakka J, Ronnholm K, Karikoski R, et al. Plasma exchange and retransplantation in recurrent nephrosis of patients with congenital nephrotic syndrome of the Finnish type (NPHS1). Transplantation 2007;83:1316-23.
98. Gadegbeku CA, Gipson DS, Holzman LB, Ojo AO, Song PX, Barisoni L, et al. Design of the nephrotic syndrome study network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. Kidney Int 2013;83:749-56.
99. Hada I, Shimizu A, Takematsu H, Nishibori Y, Kimura T, Fukutomi T, et al. A novel mouse model of idiopathic nephrotic syndrome induced by immunization with the podocyte protein Crb2. J Am Soc Nephrol 2022;33:2008-25.
100. Moller-Kerutt A, Rodriguez-Gatica JE, Wacker K, Bhatia R, Siebrasse JP, Boon N, et al. Crumbs2 is an essential slit diaphragm protein of the renal filtration barrier. J Am Soc Nephrol 2021;32:1053-70.

https://doi.org/10.3339/ckd.22.042