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# A New Approach to Idiopathic Nephrotic Syndrome

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Minimal-change disease (MCD) and primary FSGS are important causes of idiopathic nephrotic syndrome (INS) and, in the case of FSGS, end-stage renal failure. Intriguing features of these diseases include their frequent response to steroids, their association with immune abnormalities, the existence of a circulating permeability factor, and, in the case of FSGS, the tendency for disease to recur in some patients after transplantation. An article published in this issue of *JASN*[1] shows that immune reconstitution of immunodeficient mice with cells from patients with INS induces a MCD-like lesion. This new story provides further evidence for INS being a disease of the immune system.

In 1974, Shalhoub[2] proposed the now-famous hypothesis that "lipoid nephrosis," what we now call MCD, is a disorder of T cell function resulting in the production of a circulating lymphokine toxin (later termed a vascular permeability factor) based on limited humoral immunity and immune effectors in glomeruli, remissions with measles infection or with corticosteroids and cyclophosphamide, and reports of disease occurring with Hodgkin's disease or thymoma. Although we now know more about INS, we still do not know how it occurs; neither do we have targeted, effective, and nontoxic therapies. We know that the podocyte, the primary glomerular cell type affected in INS, is critical to the maintenance of glomerular structure and function,[3] and podocytes are directly affected by treatments for MCD/FSGS.[4] More-

over, some cases of "idiopathic" FSGS are due to genetic mutations in podocyte-specific proteins.[3] The recurrence of disease after transplantation, the control of posttransplantation FSGS with plasmapheresis or immunoabsorption, and the resolution of proteinuria after transplantation of nephrotic kidneys into recipients with ESRD that is not due to FSGS support the pathogenicity of this still-elusive circulating factor or factors.[5]

Given the association of MCD with allergy and atopy in children,[6] it has been hypothesized that aberrant T helper cell 2 cytokine production drives this disease. Human podocytes express receptors for IL-4 and IL-13 and respond to either cytokine,[7,8] and recent evidence in IL-13–overexpressing rats confirms IL-13 as a possible factor in MCD.[9] Although disease has been associated with raised serum or peripheral blood mononuclear cell Th2 cytokines, not all studies are concordant.[10] Assessment of immune abnormalities in patients with MCD and primary FSGS are confounded by the tendency of childhood relapses of MCD to be associated with viral infection, by questions of "cause *versus* consequence,"[11] and by differences in methods of assessing cytokine production. Models of primary INS do exist. Transfer of supernatant from lymphocytes or T cell hybridomas of patients with nephrotic syndrome[12] or a posttransplantation FSGS factor into rats results in proteinuria.[13] The Buffalo/Mna rat strain develops nephrotic syndrome that is caused by immune abnormalities, perhaps with some additional intrarenal podocytic genetic abnormality.[14,15]

In this issue of *JASN*, Sellier-Leclerc *et al.*[1] use an innovative approach, humanizing NOD/SCID mice, to implicate further an "immature" immune system in the pathogenesis of FSGS. Owing to severe combined immunodeficiency, these mice act as a "blank immunologic palette" into which human cells can be transplanted and engrafted and the resultant effects studied *in vivo*. Researchers have used these mice in studies of human lymphocyte development and HIV infection.[16] Using human CD45 as a common leukocyte marker, immune cells from patients or control subjects were able to reconstitute an immune system in these mice to some degree. CD34 defines an immature cell population that has the capacity to differentiate into T cells, B cells, or myeloid cells. Transfer of immature CD34$^+$ cells from patients with MCD or FSGS (but not control subjects) resulted in albuminuria and an MCD-like lesion in mice with electron microscopic–defined podocyte changes very similar to those seen in humans. The nature of the reconstitution was such that mature CD3$^+$ cells were not seen in the periphery, counting against a mature T cell subset being culpable, and lack of regulatory T cell function also seemed unlikely.

Progenitor CD34$^+$ cells differentiating into T lymphocytes are positively and negatively selected in the thymus. In humans, the T cell repertoire is most actively defined in early childhood, although T cell selection can occur throughout life. Data from other studies suggest that the dysregulated release of less than fully mature cells from the thymus is important in the pathogenesis if INS.[17] The validity of humanizing SCID mice

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has been questioned, because human cells from a single donor that were transferred into syngeneic NOD/SCID mice led to engrafted populations with different T cell repertoires, explained by xenoreaction-driven selection.[18] However, Sellier-Leclerc et al.[1] report that despite using different human donors with INS, all successfully engrafted mice developed albuminuria and histologic changes, strengthening the case that this model is pertinent to the study of INS. The advantages of humanized *in vivo* systems have been detailed in other disease processes.[19,20] This system, using human immune cells *in vivo*, may provide the means of defining the cellular and molecular immunopathogenesis of INS and perhaps will assist the development of more targeted interventions.

The induction of podocyte changes in a rodent does not in itself suggest pathogenetic relevance, but that these changes result from only transfer of patient cells is compelling evidence for immune dysregulation in MCD and primary FSGS. Refinement of this technically challenging model, for example by using strains of mice that lack both lymphocytes and NK cells (NOD/SCID/IL2R$\gamma^{null}$) yet develop normal lymph nodes will facilitate testing hypotheses that are generated by the discovery that immature cells may be the key.[16] Is there a thymic abnormality, as suggested by some studies?[17] Is there an immature T cell clonal proliferation in INS? Are any of the proposed soluble mediators, for example IL-13, important?[7,9] Clearly, these studies do not rule out a key role for podocytes in defining disease severity or progression—maybe a combination of immune dysregulation and a "vulnerable podocyte" is required for resistant or progressive disease. Sellier-Leclerc et al.[1] provide further support for a 33-yr-old hypothesis that has sounded attractive but has not been definitively proved. They answer some questions but raise others. Whether these findings will lead to more effective treatments is not clear, but they do add significantly to our understanding of these unusual and in some cases debilitating diseases.

## DISCLOSURES

None.

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See the related article, "A Humanized Mouse Model of Idiopathic Nephrotic Syndrome Suggests a Pathogenic Role for Immature Cells," on pages 2732–2739.