T Cells and Minimal Change Disease

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It is one of the ironies of medical practice that as physicians we can competently and confidently treat diseases of whose pathogenesis we remain woefully ignorant.

Such is the case with minimal change disease, the most common diagnosis associated with the nephrotic syndrome in children (MCNS). The disease manifestations of nephrotic-range proteinuria, hypoalbuminemia, and hyperlipidemia in such patients are typically reversible with corticosteroid therapy. MCNS has, by definition, no abnormalities apparent on analysis of kidney biopsy specimens by light microscopy. Humoral components of the immune system, such as Ig and complement, are absent on immunofluorescent analysis of cortical kidney sections. The sole abnormalities seen in the kidney are at the ultrastructural level. The most prominent of these is effacement of the visceral epithelial cell foot processes, a finding seen with many forms of glomerular pathology that are associated with nephrotic-range proteinuria. These ultrastructural abnormalities typically resolve with corticosteroid-induced clinical remissions (1).

What is the pathogenesis of this acquired and frequently reversible abnormality in glomerular ultrastructure and glomerular basement membrane (GBM) permeability? Almost 30 yr ago, R. J. Shalhoub (2) proposed that lipoid nephrosis, an older term for nil lesion or MCNS, was a systemic disorder of T cell function and cell-mediated immunity. This proposal, developed in the format of a hypothesis paper, sought to reconcile a number of clinical observations with the rudimentary knowledge of T lymphocytes that existed in 1974. Shalhoub hypothesized that the abnormal expansion of a clone of T cells might result in the production of a lymphokine toxic to the GBM, resulting in markedly altered glomerular permeability to protein. The evidence supporting this hypothesis included the observations that minimal change disease frequently remits with measles infection (viral-associated immunosuppression), that the patients are highly susceptible to pneumococcal infections (despite minimal losses of IgG in urine), that remissions are induced with corticosteroid therapy and prolonged with cyclophosphamide, and that similar lesions can occur in Hodgkin disease (2). Shalhoub additionally hypothesized that the lymphokine may exert a direct effect on the GBM or activate mesangial cells to produce a factor that altered glomerular permeability (2).

This publication preceded by over a decade the molecular definition of the T cell antigen receptor as a heterodimeric structure derived from gene rearrangements (3) and the cloning of the first cytokine or lymphokine (4). It preceded by several years the earliest attempts to characterize subsets of T lymphocytes by their functional and phenotypic heterogeneity (5,6). Shalhoub’s hypothesis has resurfaced multiple times since 1974, as clinical investigators take advantage of increased knowledge about immunology and technical breakthroughs to reexamine the role of T cells in MCNS. In 2002, it is fair to say that a role for T cells in MCNS continues to be an intriguing hypothesis that has been neither proven nor refuted. In this issue of JASN, Sahali et al. (7) describe the application of differential screening of a subtractive cDNA library to examine which, if any, T cell genes are upregulated during relapse of MCNS. Their novel findings provide intriguing additional support for Shalhoub’s hypothesis.

To understand why this is a difficult hypothesis to prove, it is helpful to step back and outline how T cells come to be implicated as necessary participants in the pathogenesis of disease. In doing this, we make a distinction between the role of T cells in providing a helper function for B cell maturation and antibody production and the role of T cells as more direct effectors of disease. Nephrologists have of course long been cognizant of the importance of humoral effectors, such as antibody and complement, in the mediation of renal injury. Recognition that activated T cells can directly mediate renal injury, lead to alterations in renal function, and be associated with renal pathologic abnormalities, such as interstitial nephritis (8), glomerulonephritis (9), and glomerular crescents (10), has not been widely appreciated among practicing nephrologists (11). Why?

Our clinicopathologic approaches to the diagnosis and classification of inflammatory renal disease have been heavily biased in favor of humoral immune reactants, such as IgG and complement. If IgG and complement are detected on immunofluorescent analysis of a kidney biopsy, they are usually presumed to be contributing to the pathogenesis of disease. (In fact experimental data would suggest that is not always the case [12]) For example, we can demonstrate that antibody reactive with GBM is present in serum, present in the renal biopsy, and associated with glomerular inflammation and alterations in GFR in patients with anti-GBM disease. In a laboratory setting, antibodies with GBM specificity can be
infused into experimental animals and elicit inflammation and proteinuria, thereby fulfilling Koch’s postulates (13).

Activated T cells are frequently present within the glomeruli and interstitial compartments of biopsies from patients with glomerulonephritis (14–16). However, unlike IgG, we cannot as readily identify T cells with the same antigenic specificity in the peripheral blood, nor, until more recently, could we definitively demonstrate with adoptive transfer that T cells with specificity for an antigen expressed within the glomerulus mediate glomerulonephritis (17). T cell Ag receptors recognize short linear peptides, derived from processed antigen, in association with class I or class II MHC molecules on the surface of antigen-presenting cells or target cells (18). Therefore, to identify T cells of a given Ag specificity in the peripheral blood, knowledge of the epitope recognized is required, and that antigen must be in a form that can be recognized by T cells. Presently, an approximation of numbers of T cells reactive with a particular antigen can be experimentally determined using immunostaining with MHC tetramers complexed with Ag (19). However, such a technique is not yet available for routine clinical diagnosis.

What about minimal change disease? In this form of nephrotic syndrome, T cells are only rarely encountered within the glomerular compartment (20). Thus it is difficult to incriminate them given their relative absence in the glomerulus. But Shalhoub’s hypothesis was that clinical MCNS resulted from “episodic or sustained domination by a clone of T cells,” which secreted a lymphokine toxic to the GBM, thereby altering permeability to protein (2). Are there differences in circulating T cells in MCNS patients?

In patients with active MCNS, there may be alterations in T cell subpopulations in the peripheral blood, including increased numbers of CD4+CD45RO+ and CD8+CD45RO+ memory subsets (21). Earlier studies supported enhanced expression of the IL-2R on unstimulated T cells from patients with active minimal change disease (22). This is intriguing, given the number of recent studies revealing the regulatory and inhibitory functions of this CD4+CD25+ subset of T cells (23). A number of functional assays of T cells are abnormal in patients with active minimal change disease. Cell-mediated immunity, if assessed by delayed cutaneous hypersensitivity reactions or recall responses to common antigens, is depressed in these patients (24). These depressed responses are associated with “suppressor factors” in both urine and serum (25). Proliferative responses to mitogens are improved when lymphocytes are cultured in normal plasma, whereas plasma from nephrotic patients suppresses the blastogenic response of lymphocytes to mitogens and common recall antigens. These studies suggest the presence of a soluble factor inhibiting T cell proliferation (24,26). Serum immunoglobulins are also abnormal in patients in relapse and are characterized by depressed IgG, and elevated IgM (27).

Another investigative focus linking activated T cells to MCNS has been on the soluble factors produced by activated T cells that alter glomerular permeability to protein. Such factors, found both in bulk cultures of activated T cells from MCNS patients (28) as well as T cell hybridomas generated from MCNS patients in relapse, induce abnormal urinary protein excretion when injected into rats (29). Serum from patients with MCNS alters the albumin permeability of rat glomerular epithelial cell monolayers (30). The identity of the factor(s) has remained enigmatic. Recent studies have suggested that IL-4 and IL-13 are overexpressed in patients with steroid-responsive nephrotic syndrome in relapse (31). It is of interest that these same cytokines can increase transcellular ion transport over glomerular visceral epithelial cell monolayers. These effects on ion transport are associated with basolateral secretion of lysosomal proteases, such as procathepsin L (32). Such effects may link abnormal cytokine expression to altered glomerular permeability.

A common feature of the immune abnormalities documented above in patients with active MCNS is that the investigators studying those abnormalities made choices about what to measure. Assessments of phenotypic or functional differences between T cells from active MCNS patients and those in remission or normal controls were conducted with a hypothesis that the measured parameter might be different in relapse versus remission. The beauty of the approach taken by Sahali et al. (7) in this issue of JASN is that the data generated is largely independent of preconceived determinations about which genes might be differentially expressed in MCNS relapse versus remission. Using this approach, the investigators identified a number of differentially expressed transcripts relevant to T cell activation, signal transduction, cell division, and transcriptional activation. Confirmation that some of these genes are upregulated in MCNS relapse compared with remission off corticosteroids was obtained by assessing RNA and/or protein expression in peripheral blood mononuclear cells from other MCNS patients (7). The use of patients with membranous nephropathy (although the clinical status of those patients and their therapy was not explicitly described) presumably provides a control for other proteomic states. Some of the data, such as upregulation of c-maf expression and downregulation of IL-12Rβ2 during relapse could fit well into previously proposed paradigms of “Th2-bias” in patients with active MCNS.

What are the limitations of the present study by Sahali et al.? This type of study is not designed to tell us what has elicited T cell activation or even whether the apparent T cell activation is responsible and required for the proteinuria. One could alternatively envision an upstream pathogenetic event responsible for two independent events, i.e., T cell activation and proteinuria. In that case, the current findings may largely represent an epiphenomenon. However, the authors are to be commended for their dedication to defining the immunopathogenesis of this disease by using state of the art techniques. When viewed in conjunction with their recent findings of alterations in the NF-κB/IκBα system in active MCNS (33), the findings are highly intriguing and should serve to extend the lease on the T cell dysfunction theory of lipid nephrosis.

References


