Host Immune Deficiency in Immune Complex Nephritis

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ABSTRACT

Evidence is reviewed that indicates that an immune deficiency state may underlie patients with immune complex nephritis. Studies in several laboratories provide data that show defective immune function in patients with nephritis at the following loci: defective immunoglobulin production, impaired monocyte Fc and C3b receptor function, diminished complement biosynthesis, and decreased mesangial cell colony-stimulating factor-1 biosynthesis. Aberrant monocyte function may be an important common denominator. The validation of this hypothesis has important implications for therapeutic strategies.

Key Words: Nephritis, Immunity, Macrophage

In 1974, Peters and Lachmann (1) proposed that immune deficiency states may underlie patients with nephritis. The recent description of patients with HIV infection who develop various forms of immune complex nephritis (2) emphasizes the need to revisit the issues raised by this hypothesis. When this hypothesis was promulgated in 1974, there was scanty evidence in the human subject to substantiate its main tenets. Since then, studies have been done that have provided substantial support for such a hypothesis, although lately, there appears to have been a waning of interest. The purpose of this review is to refocus interest in an area of host biology that is of potential importance in the genesis of nephritis.

Our formulation of the hypothesis begins with an iteration of normal host homeostatic mechanisms by which immune complexes generated in response to a foreign antigen are eliminated. As a preamble, it may be stated that an immunologically deficient host such as a patient with HIV is rendered more susceptible to a variety of infective organisms because of a deficient immune response, as demonstrated by a variety of in vitro and in vivo techniques (3). Such infective organisms may themselves be injurious to the kidney or may provoke the formation of antibodies, leading to antigen-antibody complexes. In the HIV host, it is apparent that the initial infection of the host by the virus can provoke an antibody response to the inciting agent (3), leading to the formation of HIV-anti-HIV complexes; the immune deficiency state produced by the infestation leads to the intercurrent invasion of the host by other microbial organisms, which can lead to secondary (and tertiary) cycles of antigenic challenges followed by the relevant antibody responses and subsequent formation of their respective immune complexes. It is conceded that only a minority of these patients develop immune complex nephritis, suggesting the role of other factors in the genesis of this form of renal disease.

When the host is exposed to an antigen, it mounts an immune response that attempts to eliminate this foreign substance. There are at least two processes that are critical in this respect. The nature and magnitude of the antibody response are one of these. Of equal importance is the physiologic state of the mononuclear phagocyte system that possesses Fc and C3b receptors and that is of pivotal importance in the clearance of circulating antigen-antibody complexes. The deposition of such complexes in the kidney occurs when the complexes bypass this buffering system. It follows from these considerations that immune complex nephritis may arise when there is an aberration in the functions of any of these compartments. Thus, if the antibody response is defective, such that there is relative antigen excess, allowing the formation of complexes that are not readily cleared by the mononuclear phagocyte system, or if the phagocyte system itself is defective, either intrinsically or secondarily as a result of saturation of its receptors, complexes will deposit in the kidney. Finally, there are also important mechanisms that mediate the removal of tissue complexes, and if these mechanisms operate inefficiently, there will be a persistence of these phlogistic substances in tissue sites.

HOST IMMUNE RESPONSE

The studies of Germuth and Rodriguez (4) showed very clearly that the magnitude of the antibody response was a critical determinant in the induction of nephritis (it is also acknowledged that other characteristics of the antibody such as charge and affinity are also important determinants (5)). Thus, a suboptimal antibody response was required for the development of immune complex nephritis. Their investigations also demonstrated that the histologic expression of nephritis depended on the vigor of the antibody response. Data on the immune response of human subjects with nephritis have been obtained by several investigators. Studies on patients with lupus nephropathy showed that those developing membranous nephropathy had lower titers of anti-DNA anti-
body (6). In vitro studies on the responses of lymphocytes challenged with a polyclonal stimulator such as pokeweed mitogen revealed that patients with membranous nephropathy were deficient in terms of immunoglobulin mitogen production; furthermore, it was shown that this defect was mediated by suppressor monocytes, because if the mononuclear cells were depleted of monocytes, the suppressive effect could be nullified (7). Confirmation for these results has been obtained by other investigators who have extended their studies to patients with membranoproliferative glomerulonephritis and shown that a similar defect exists in this population of patients as well (8). It is important to address the relationship between the finding of a reduced antibody response in subjects with membranous nephropathy and the observation that the membranous lesions of Heymann's nephropathy arise from in situ immune complex formation. The elegant studies from the laboratory of Couser and Salant have yielded invaluable insights into this mechanism of glomerular injury (9). In human membranous nephropathy, the infrequency with which immune complexes are found in the circulation (10,11) points to in situ mechanisms of immune injury. It is also possible that diverse mechanisms may be operative in the different subpopulations of patients with this type of renal pathology (12). In the case of in situ immune complex formation, a reduced antibody response would facilitate the implantation of antigen, allowing the subsequent fixation of antibody to the implanted antigen; thus, the results of the studies of the antibody response of patients with this disorder are compatible with either mechanism of renal injury.

**FC AND C3B RECEPTOR FUNCTION**

The preeminent role of the mononuclear phagocyte system in uptake and processing of infused immune complexes has been demonstrated by experimental studies from the laboratory of Mannik et al. (13,14). Thus, it was shown that the bulk of such macromolecules was taken up by the reticuloendothelial system and if the properties of the complexes were modified so that they escaped processing by this system, there would be enhanced deposition in the kidney. The validity of these observations has been confirmed by studies that showed that if the functions of the mononuclear phagocyte system were stimulated by various substances, there would be enhanced clearance of the antigen-antibody complexes with reduced deposition in the kidney (15,16). Studies in patients with various forms of glomerulonephritis have also been accomplished. By the use of labeled sensitized erythrocytes antigen-antibody complexes, it was shown that there was impaired clearance of these substances in patients with systemic lupus erythematosus and that this defect correlated with the amounts of complexes found in the circulation (17). Similar results have been observed for patients with immunoglobulin A (IgA) nephropathy and membranous nephropathy (18,19). In the case of IgA nephropathy, studies have also been done with labeled IgA-IgG aggregates that have shown a delayed clearance of these proteins in the circulation of the patients, confirming a defect of macrophage function (20). Of interest, patients with the HLA phenotype HLA-B8/DRw3 have impaired clearance of immune complexes (21).

Studies have also been done using an in vitro technique, measuring the ability of isolated human monocytes to phagocytize sensitized erythrocytes and latex beads. It was shown that 4 of 10 patients with a form of mesangial proliferative glomerulonephritis had a demonstrable defect in phagocytic function (22). It is important to recognize that this defective Fc receptor function may have other consequences in addition to the impairment of the removal of circulating antigen-antibody complexes. Thus, studies have demonstrated that tissue immune complexes were removed in part by monocytes accumulating in the glomeruli so that the impairment of Fc receptor function could more readily allow the persistence of such tissue complexes (23). Recent studies using a model of chronic serum sickness showed that glomerular macrophage phagocytic function decreased as the host progressed to a severe stage of the illness (24). Autimmune mice have also been examined and determined to have a defect in the degradative capacity of their macrophages, a function that was demonstrated to be under the control of lymphokines (25).

In addition to the Fc receptor system, the erythrocyte CR1 system has been shown to be of importance in the disposition of immune complexes in the primate (26-28). In brief, immune complexes that are opsonized with C3b become bound to erythrocytes that express CR1 (the receptor for C3b); they are then transported to the liver and spleen where the immune complexes are stripped from the erythrocytes and taken up by the cells of the mononuclear phagocyte system. The erythrocytes become available once more for this transport function. It has been shown that if this function is interfered with, immune complexes become trapped in vulnerable locations such as the kidney. Germane to this hypothesis, defects in C3b receptor expression and/or function have been found in patients with systemic lupus erythematosus (SLE) (29,30) and IgA nephritis (31,32).

**COMPLEMENT BIOSYNTHESIS**

The third locus in which a defect of immune function has been identified is in the biosynthesis of complement. The association of inherited complement deficiency states (particularly of the components that contribute to the formation of C3b) and the development of lupus-like syndromes and/or nephritis/vasculitis are now widely recognized and have been reviewed in depth recently (33). These clinical associations have indicated that a complement deficiency predisposes to the development of lupus-like
syndromes, with concomitant nephritis in many instances. The exact reasons for this association are uncertain, but certain productive hypotheses have been advanced. A defect in such an important humoral system of host defense may allow the persistence of the etiologic agent responsible for the development of immune complex disease. Second, complement may have an important function in the solubilization of tissue antigen–antibody complexes (34): the intercalation of C3b into the lattices of antigen–antibody complexes prevents the formation of large insoluble immune complexes and favors their dissociation (35). Finally, studies of linkage between HLA and complement component deficiency studies show a linkage of some complement component deficiencies to certain HLA haplotypes (36). This linkage may suggest that complement deficiency states may occur in individuals with genes that determine special classes of immune complexes, resulting in the generation and persistence of immune complexes. More recently, it has also been suggested that complement may be of importance in opsonizing complexes, thereby allowing them to bind to erythrocytes, and, in this way, preventing them from depositing in vulnerable sites (37). A recent investigation demonstrated the importance of complement as a determinant of the site of localization within the glomerulus—thus, in the absence of C3, complexes localized in the subendothelial location, whereas when C3 was present, complexes migrated to the subepithelial space (38). Although the total absence of a complement component highlights the association between complement deficiency and nephritis, there is evidence that patients with many forms of nephritis have defective complement biosynthesis.

Early studies performed in several laboratories investigated the metabolism of radiolabeled complement component in patients with various forms of idiopathic nephritis and in lupus erythematosus and found a defect in complement biosynthesis in a significant proportion of the subjects (39,40). Sliwinska and Zwaifler (40), studying C3 metabolism in patients with SLE, found decreased synthesis in five of six patients. Peters et al. (41) obtained evidence of diminished radiolabeled C3 synthesis in a study of 15 patients with membranoproliferative glomerulonephritis. Several experimental and clinical observations shed light on the possible mechanisms involved. In an experimental model of acute serum sickness nephritis in rabbits, Bartolotti and Peters (42) showed that in rabbits decomplemented by cobra venom factor, the rate of clearance of radiolabeled renal bound antigen was significantly decreased compared with controls. Their findings suggest that in immune complex nephritis, the clearance of deposits in the kidney is complement dependent.

A clinical study emphasized the importance of this function of complement in human disease. Schifferli et al. (43) examined the solubilizing capacity in many of the patients studied. Solubilization capacity also correlated with disease activity in patients with SLE, vasculitis, and poststreptococcal glomerulonephritis. It is germane to emphasize that because many complement components are synthesized by monocytes/macrophages, a failure of local delivery of complement in this regard will have even more profound consequences in terms of the removal of tissue deposits (44).

**MESANGIAL CELL FUNCTION**

Finally, an abnormality that has been discerned in recent studies of autoimmune mice is an impairment in the capacity of the mesangial cell to locally activate macrophages. Recent studies have demonstrated that the mouse contractile mesangial cell produces a factor (colony-stimulating factor-1, CSF-1) that activates macrophages and induces their replication (45–47). Previous studies have shown that the principal effector cell infiltrating the glomerulus is the monocyte/macrophage (48,49). The infiltrating monocyte/macrophage releases various factors including interleukin-1 that stimulate mesangial cell proliferation (reviewed in Refs. 50 and 51). Under these circumstances, it can be envisaged that the mesangial cells will release more of the CSF-1-like factor, which activates macrophages to degrade localized immune complexes. A defect in the mesangial cell production of this CSF-1-like factor will favor the persistence of immune complexes in the glomeruli. Such a defect has in fact been found with the mesangial cells of the MRL/1pr/1pr strain of mice, which are prone to develop autoimmune nephritis (52,53). Finally, it is acknowledged that the cellular events involved in the genesis of nephritis are complex and involve the mesangial cell in a variety of interactions with different cells, the course of which is modulated by many factors, among which are cytokines and adhesion cell molecules (54–56).

In summary, there is evidence that supports the hypothesis that an immune deficiency state may underlie patients with various forms of nephritis. Figure 1 summarizes in diagrammatic form the sequence of events that occurs when the host encounters an antigen together with a delineation of the loci in which a defect in immune function has been uncovered. So far, defects at four loci have been determined: a defect in immunoglobulin (and antibody) production mediated by suppressor monocytes, a monocyte Fc and C3b receptor defect, a defect in the biosynthesis of complement, and a defect in mesangial cell CSF-1 production (which locally activates glomerular macrophages). It is proposed that future studies of such patients may uncover defects at other loci, providing data that will strengthen the hypothesis. It is acknowledged that such immune defects may not be primary and may arise from the nephrotic state (or other physiologic disturbance). Even if this were the case, the immune defects triggered would have the same consequences in terms of the pathophysiology of ne-
Figure 1. Immune deficiency in nephritis. A schematic representation showing loci of deficient immune function in the sequence of events leading to immune complex nephritis. Stippled lines denote reduced concentration/function/production of the designated parameter. RBC-CR1, erythrocyte complement receptor type 1; FcR, Fc receptor; MPS, mononuclear phagocyte system; C, complement.

phritis and would be of considerable significance. It must also be emphasized that the presence of the host deficiency merely provides the background for the development of nephritis. Other factors are also of importance in contributing to the development of this form of renal disease and in influencing the nature of the lesion produced. Thus, the host must encounter the appropriate antigen; factors such as the types of immune complexes generated (charge, size, etc.) and the nature of the effector cells together with the responses of the mesangial cells will determine the histologic expression of nephritis.

There are several implications of the results obtained from the various investigations cited. In addition to confirming the postulate originally advanced by Peters and Lachmann (1), they focus attention on the finding that the defects determined so far are at the level of the monocyte. It suggests that the causative agent (whether chemical or microbiologic) may affect the monocyte; the responses of this cell may determine the nature of the immune disturbance, resulting in nephritis. It is likely that further studies on monocyte physiology in nephritis will be productive. The corollary of these conclusions is that strategies of treatment may need to be revised and that immunostimulation may be more effective in achieving success in the resolution of nephritis. The partial success obtained by current methods using immunosuppressive agents do not necessarily vitiate the notion of immune deficiency as an underlying predisposition for the development of nephritis; thus, immunosuppressive agents may act in part by altering the ratio of antigen to antibody in favor of antigen excess, a physiologic state that has been shown in animal models to lead to the solubilization of tissue complexes (57). In terms of immunostimulation, it can be envisaged that when specific agents are available, stimulation at the precise locus of deficiency may be the ideal form of therapy in this form of illness. As an example, CSF-1 is an agent that may be considered as a therapeutic agent because of its macrophage-activating properties. Finally, it is suggested that one of the prerequisites for the evaluation of a patient with nephritis is a comprehensive work-up of his or her immune status to determine the precise locus of the immune deficiency.

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REFERENCES


