REVIEW ARTICLE

Glomerular Diseases and Renal Transplantation: Pathogenic Pathways and Evolution of Therapeutic Interventions

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ABSTRACT

Glomerular diseases and renal transplantation are the main fields of nephrology in which the immune system plays a prevalent role. Glomerular diseases have traditionally been attributed to auto-immune conditions, whereas allograft rejection has been considered an allo-immune response. However, common immunopathologic mechanisms that include Toll-like receptors, complement and B-cell activation, as well as genetic and infectious factors appear to be involved in the pathogenesis of both entities. Novel therapeutic regimens directed against specific targets of the immune system show promising results in glomerulopathies as well as in renal transplantation.

IMMUNE renal injury is the result of an auto-immune or allo-immune response. In the case of auto-immune injury, the immune system attacks self-antigens (auto-antigens), whereas in the second case, the immune response is directed against foreign antigens (allo-antigens) of invading pathogens.

Glomerular diseases and renal transplantation are the main fields of nephrology in which the immune system plays a prevalent role. However, until recently, the pathogenetic mechanisms of these two entities were considered to be distinct entities because of the prominent role of auto-immunity through antibody production and immune complex deposition in glomerular diseases and allo-immunity in renal transplantation.

Moreover, histologic features differ between glomerular diseases and transplantation; in glomerular diseases, histologic damage involves primarily the glomeruli and secondarily the tubulo-interstitium and small vessels, whereas in transplantation, allograft injury comprises primarily the tubulo-interstitium and the vessels, whereas damage of the glomeruli is manifested either as transplant glomerulopathy or as primary glomerular disease recurrence in the renal allograft.

However, recent research has shown that the pathogenetic mechanisms in both conditions share common pathways and that there is cross-reaction between innate and adaptive immunity as well as between auto- and allo-immunity [1].

Pathogenesis

Innate and Adaptive Immunity and Complement Activation. Proper and balanced function of the immune system ensures adequate protection against exogenous pathogens but also against endogenous disease-causing agents. Glomerular diseases have been considered traditionally as auto-immune diseases because the main pathogenic mechanism involves (auto-) antibody production and immune complex formation. On the other hand, renal transplantation is considered as an allo-immune condition, in which allograft damage is the result of direct reaction of immune cells toward the graft.

The innate immunity system provides the first line of defense against "danger signals" such as microbes via cellular and humoral mechanisms. Innate immunity is rapid but specific; it acts through the recognition of pathogens presented by antigen-presenting cells (APCs; ie, macrophages, dendritic cells, and leucocytes) and their susbsequent destruction through opsonization and phagocytosis. Recent studies have highlighted the important role of

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0041-1345/17
http://dx.doi.org/10.1016/j.transproceed.2016.11.035

Toll-like receptors (TLRs) and the complement in the induction and evolution of the glomerular damage [2,3].

Regardless of the etiology, the first step in the activation of innate immunity is the recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) by macrophages, dendritic cells, neutrophils, and natural killer cells (NK) [4]. PAMPS and DAMPS are released either from dead parenchymal cells or during the remodeling process of the extracellular matrix [5,6].

The innate immune response leads to immediate complement activation through the lectin pathway and generation of C5a and C5b-9. These two factors cause the release of inflammatory mediators by all cells, including glomerular cells, and contribute thereby to the development of glomerular injury. Furthermore, TLRs bind to PAMPs or DAMPs on circulating inflammatory cells and on resident glomerular cells. TLR activation induces phagocytosis, cytokine and chemokine release, and inflammatory mediators that cause glomerular injury [4,7].

TLRs are expressed in tubular epithelial cells and podocytes. TLR4 activation leads to the development of nephrotic syndrome in animal models [8], whereas activation of TLR2 favors the development of proteinuria in experimental models of lupus nephritis [9].

The role of complement activation in glomerular diseases has been thoroughly investigated. Complement can be activated via the classic pathway in immune complex–mediated diseases such as lupus nephritis and cryoglobulinemic nephritis. The alternative pathway of the complement cascade is involved in the pathogenesis of renal damage in ANCA-associated small vessel vasculitis (AASV). Former membrano-proliferative GN type II, now according to the new classification named "dense deposit disease," and recurrent atypical hemolytic uremic syndrome (HUS), are both triggered by uncontrolled activation of the alternative complement pathway. These disorders have genetic etiology and are attributed to decreased expression of factors that inhibit complement activation, such as Factor H. In IgA, glomerulonephritis complement activation via the lectin pathway is likely to contribute to the evolution of the disease [4,10].

If the antigenic factor persists, TLRs activate adaptive immunity. CD4 T-helper cells differentiate into subgroups of T cells that promote inflammation (Th1, Th2, Th17). B cells are activated and produce antibodies. The latter generate immune complexes, in which TLRs and the complement system result in an amplification loop [4].

Adaptive immunity is of particular importance in kidney transplantation. Allograft injury is the result of T-cell activation in response to the presence of allo-antigens, through direct or indirect allo-recognition by APCs. Activated T cells infiltrate the renal tissue and induce cellular rejection [1].

Recent studies in the field of renal transplantation emphasize the role of innate immunity triggered by the adaptive response. The expression of TLR4 increases in deceased renal allografts grafts, thus contributing to ischemia-reperfusion injury. TLR4 suppression appeared to be associated with immediate graft function [11]. Activation of TLRs increases the immunogenicity of the kidney, enhancing the activity of T lymphocytes, which subsequently infiltrate the kidney tissue and destroy it [12]. Complement activation via both the classic pathway and the lectin pathway is also implicated in the pathogenesis of ischemia-reperfusion injury. Mice with complement deficiency are protected against ischemia-reperfusion injury in the renal graft [13].

Additionally, complement activation is essential in humoral, antibody-mediated rejection (AMR), in which there is deposition of the C4d component of the classic pathway in peritubular capillaries and glomeruli [14]. Finally, complement activation is involved in cellular rejection through release of C3a and C5a components, which enhance the activity of APCs, and act directly on T lymphocytes. Consequently, the differentiation of T-helper cells to Th1 cells induces the process of rejection [13,15].

B-Cell Activation and Antibodies. Circulating antibodies are implicated in the induction of damage in both glomerular diseases and in transplantation. Different functions of B cells contribute to the development of autoimmunity.

Auto-antibodies that bind to self-antigens are secreted, leading to the deposition of immune complexes. Circulating complex or in situ complex formation activates the classic pathway of the complement cascade and initiates the inflammatory process. Proteolytic enzymes and inflammatory cytokines are released, whereas effector cells such as neutrophils and NK cells are attracted to the site of injury. Furthermore, immune complexes can directly bind to effector cells, activating the antibody-dependent, cell-mediated cytotoxicity (ADCC) [16].

Antigen presentation is facilitated by immune complex binding to the FcR of monocytes and dendritic cells. This process enables successful activation of T lymphocytes with a lower antigen concentration. [17].

Antigen presentation by B cells is low, especially when antigen presentation is low [18].

The most typical model of auto-antibody–mediated glomerulopathy is idiopathic membranous nephropathy. In membranous nephropathy (MN), recent and former studies have identified several podocytic antigens as targets of auto-antibodies. In 1959, Heymann et al [19] demonstrated an experimental model of membranous glomerulopathy, the model of passive Heyman nephritis. In 1982, a large membrane glycoprotein also known as megalin was identified as the auto-antigen responsible for Heyman nephritis [20]. Another important finding was that activation of complement was also required for the development of proteinuria. The first evidence of in situ immune complex formation was established by Debiec et al [21]. They described a case of neonatal nephrotic syndrome and biopsy-proven membranous nephropathy in a newborn whose mother was genetically deficient in an enzyme expressed on podocytes, neutral endopeptidase (NEP). Circulating anti-NEP antibodies from presensitization of