Virus-Induced Cellular Immune Mechanisms of Injury to the Kidney

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Cellular immune systems play an important role in determining renal outcomes in virus-induced kidney diseases. Highlighted briefly are five different locations along the development of adaptive immune responses to viral infection that may promote injury to the renal parenchyma and the loss of renal function. This may occur because adaptive immune cells directly target infected renal parenchymal cells or because the kidney becomes a bystander organ of adaptive immune cell–mediated injury. Examples from recent studies are provided to illustrate how this may lead to clinically relevant renal disease.


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ISSN: 1555-9041/204–S0002
Figure 1. Simplified schema of an adaptive immune response to a viral infection. A dendritic cell (DC) that has captured viral antigen migrates from the periphery into a secondary lymphoid organ such as the spleen or a lymph node. The DC presents the viral antigen for recognition by naïve CD4+ and CD8+ lymphocytes to initiate a T helper type 1 (Th1) immune response to the virus. Naïve CD4+ lymphocytes that recognize the antigen proliferate and differentiate into CD4+ Th1 lymphocytes, which can further stimulate viral antigen-specific B lymphocytes and CD8+ lymphocytes to differentiate into plasma cells and cytotoxic T lymphocytes (CTL), respectively. CD4+ Th1 lymphocytes will also activate mononuclear phagocytes (MΦ) that present viral antigen in the periphery. Five locations marked by the boxed numbers 1 through 5 along this adaptive immune response have been implicated in promoting bystander or direct injury to the renal parenchyma and include the following: 1, pattern recognition of viral products by dendritic cells; 2, B lymphocyte/plasma cell responses; 3, activation of mononuclear phagocytes; 4, encountering viral antigen in the periphery by T lymphocyte effectors; and 5, CTL responses. The mechanisms of bystander injury to the renal parenchyma, represented by 1 through 3, can initiate within and/or outside the kidney, whereas the bystander injury, represented by 4, occurs within the kidney. The mechanism of direct injury to the renal parenchyma, represented by 5, occurs within the kidney.

Hyperactive B Lymphocyte Responses

The ability of B lymphocytes to produce neutralizing antibodies against viruses is an important determinant of adaptive immune responses to control, eliminate, and protect from viral infections (1). CD4+ Th1 lymphocytes that recognize viral antigen that is presented by B lymphocytes in the context of their surface Ig secrete cytokines that will promote the proliferation and Ig class switching of these B lymphocytes (Figure 1). If effective, then the result is plasma cells that produce high-affinity, neutralizing, opsonizing, and complement-activating antibody that is directed against viral epitopes.

This Th lymphocyte–dependent B lymphocyte response, however, may become hyperactive and, in some cases, cause a loss in tolerance through mechanisms such as molecular mimicry and epitope spreading (9). In the former possibility, a nonspecific polyclonal hypergammaglobulinemia of viral infection can occur (9), leading to sequelae in the kidney such as distal renal tubular acidosis (10) or the renal disease manifestations of cryoglobulinemia. In the latter possibility, antibody that is directed against self-antigen may be produced (9), as was recently found in some HIV-infected patients who developed antibodies that were directed against extracellular components of the glomerular basement membrane (11). Thus, in response to a viral infection, hyperactive or aberrant B lymphocyte responses may produce antibody that induces bystander injury to the kidney.

Excessive Activation of Mononuclear Phagocytes

Th1 lymphocytes that encounter mononuclear phagocytes (MΦ) that present viral antigen in the periphery (Figure 1) will classically activate these MΦ to perform their own effector functions (1). This includes the production of reactive oxygen intermediates, nitric oxide, and lysosomal enzymes; the secretion of several proinflammatory cytokines and growth factors; and the upregulation of co-stimulatory molecules. These effector functions can play an important role in inactivating virus that is sequestered with Mφ, in amplifying adaptive immune responses, and in promoting tissue repair. However, if excessive or poorly resolving, then tissue injury may result from these MΦ effector functions.

A dramatic example of the potential for bystander injury to the kidney by MΦ is presented by the hemophagocytic syndrome (HPS), a severe inflammatory state that is caused by the excessive activation, proliferation, and infiltration of multiple tissues by nonmalignant MΦ (12,13). HPS can be genetic in origin, or it may develop secondary to infection, malignancy, or autoimmune disease (12,13). HPS is a recognized complication of infection by several viruses, including Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus, HIV, and parvovirus B19 (12,13). Renal sequelae can include acute renal failure secondary to acute tubular necrosis, and, recently, an association between HPS and podocyte injury was found (14). Several patients with HPS and proteinuria were discovered to have minimal-change disease, FSGS, or collapsing glomerulopathy on kidney biopsy (14). This podocyte injury may have occurred secondary to the cytokine storm that often develops in patients with HPS (12–14).
**Encountering Viral Antigen in the Kidney**

T lymphocyte effectors that have been generated during the adaptive immune response will exit secondary lymphoid organs to traffic in search of viral antigen (Figure 1) (1). This viral antigen may be associated with and presented by nonimmune and/or immune cells that reside anywhere in the periphery. CD4+ Th1 lymphocytes that recognize viral antigen that is presented by MHC class II molecules, which in the kidney are expressed by endothelial cells in glomeruli but have not been consistently detected on other renal parenchymal cells, will be activated to perform localized effector functions that are designed to eliminate virus at the site of antigen encounter. CTL that recognize viral antigen that is presented by MHC class I molecules, which in the kidney can be expressed by all renal parenchymal cells, will directly kill the cell that presents the viral antigen (discussed next).

The recent discovery of the contiguous renal DC network raised the possibility that viral antigen may be encountered by T lymphocyte effectors within the kidney apart from the parenchymal cells of the nephron (15). One major immunologic function of tissue-resident DC is to survey for, scavenge, and present foreign antigen, whether produced locally or arriving from distant sources, in the context of surface MHC class II molecules (16,17). DC may also present foreign antigen that is produced via intracellular synthetic pathways in the context of surface MHC class I molecules. In contrast to conventional models (Figure 1), however, antigen-bearing renal DC may not receive cues to traffic out of the kidney after taking up foreign antigen (18). Thus, renal DC may scavenge and present viral antigen for recognition within the interstitial compartment of the kidney. This may be a potent recipe for organizing “nephron-associated lymphoid tissue” if trafficking T lymphocyte effectors encounter these renal DC, a potentially causative mechanism for acute and chronic virus-associated interstitial nephritis. Indeed, this phenomenon has already been demonstrated in the lung, where marked lymphoid organization within the interstitial spaces between the airways and the blood vessels can occur (19).

**Direct Injury: Targeting by CTL**

A robust CTL response is required to eliminate cells that harbor infectious virus (1). The interaction between CTL and infected cells is MHC restricted. If a CTL recognizes viral antigen that is presented in the context of MHC class I molecules on the surface of an infected cell, then the CTL will directly target the infected cell by elaborating perforin, granulysomes, and other factors that directly kill the infected cell. It is interesting that despite the number of different viruses that have been detected within renal parenchymal cells, little is known about the role of CTL responses in targeting these cells during adaptive immune responses.

Polyomavirus-associated nephropathy is a major cause of kidney allograft dysfunction, and recent studies indicate that CTL responses may play a “paradoxic” role in causing allograft failure (20,21). Under immunosuppressive drug regimens that are used to prevent rejection of kidney allografts by the host, reactivated BK virus can induce cytopathic and inflammatory injury to the renal epithelium that closely mimics rejection (20,21). One recent study found that during the tapering of immunosuppression to allow adaptive immune responses to mount against reactivated virus, allografts that were more closely matched to the host at MHC class I loci fared worse than those that were not as closely matched (22). This suggested that CTL responses were more effective at killing infected renal epithelial cells and paradoxically promoting a further loss of renal function in MHC class I–matched allografts with polyomavirus (22). This is reminiscent of immune reconstitution inflammatory syndromes that can occur after initiation of antiretroviral therapy in HIV-infected patients, in which reconstituted adaptive immune responses to an existing burden of foreign antigen (e.g., from mycobacterium tuberculosis) can lead to inflammatory injury to organs, including to the kidney (23).

**Conclusion**

In attempting to contain viral infections, adaptive immune responses can promote injury to the kidney. We have discussed in this brief overview several ways whereby adaptive immunity can directly and indirectly cause the loss of renal function. Future research should provide approaches to prevent, limit, or reverse this immunologic injury to the kidney in patients who are infected with viruses.

**Acknowledgments**

P.J.N. is supported by National Institutes of Health grant DK065498. The discussion was presented at the symposium “Basic Science for Clinical Nephrologists—Mechanisms of Viral Injury to the Kidney” at the 39th Annual Meeting of the American Society of Nephrology.

**Disclosures**

None.

**References**

of B7–1 in podocytes is associated with nephrotic syndrome. J Clin Invest 113: 1390–1397, 2004


