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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Cellular immune responses that are effective at combating viral infections often result from the coordinated action of both the innate and adaptive arms of the immune system (1). If a virus breaches physical barriers to infection that normally are provided by the skin and the mucosa, then the activity of immune cells (e.g., natural killer cells, granulocytes) and extracellular factors (e.g., lysozyme, complement) of the innate immune system may be sufficient to halt any further infection by the virus. If the virus escapes these innate immune responses, then adaptive immune responses are induced to try to contain the virus. In contrast to innate immune responses, these adaptive immune responses demonstrate specificity, discrimination, and acquired “memory” for distinct viral molecules (i.e., viral antigens), and the ability to respond more vigorously after repeated exposure to these same viral antigens. The effector phases of adaptive immune responses are coordinated by lymphocytes and their products, and may eliminate the virus from the host, primarily by generating neutralizing antibody that is specific for the virus and CD8+ cytotoxic T lymphocytes (CTL) that directly kill virally infected cells. These adaptive immune responses may also prevent future infections by the same virus.

In the following brief discussion, we highlight specific cellular immune mechanisms of injury to the kidney that can occur during the development of adaptive immune responses to viral infections. Figure 1 depicts a simplified schema of an adaptive immune response to viral infection and five different locations along this coordinated response where activation of adaptive immune mechanisms of injury to the kidney (1,4–6).

Bystander Injury

Pattern Recognition of Viral Products

Viruses encode products that can be recognized by immune and nonimmune cells as pathogen-associated molecular patterns (PAMP), structural motifs that serve as “danger” signals to the host indicating the presence of virus (1,4,5). PAMP also exist on a diverse repertoire of other nonviral molecules, including factors that are elaborated by damaged or stressed cells (e.g., heat-shock proteins) and by other microbes (e.g., LPS from bacteria), and play a similar role in alarming the host to environmental insults (4). The best characterized receptors for PAMP are the Toll-like receptors (TLR) (1,4,5). At least four TLR can recognize viral PAMP (1,4,5). TLR3 can recognize double-stranded viral RNA, TLR7 and TLR8 can recognize single-stranded viral RNA, and TLR9 can recognize unmethylated dinucleotide motifs in viral DNA (1,4,5). Engagement of these and other TLR on dendritic cells (DC) is an important step in determining whether DC will induce T helper type 1 (Th1) adaptive immune responses to viral infections (Figure 1) (6).

Multiples studies have now demonstrated that TLR-mediated activation of immune cells both within and outside the kidney by viral products can induce bystander injury to the renal parenchymal in renal diseases that are not conventionally considered to be of viral origin (4,5). One recent study nicely illustrates this (7). Administration of CpG-DNA, a ligand for TLR9, was capable alone of triggering proliferative lupus nephritis (i.e., a “lupus flare”) in mice that were prone to the...
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 T 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 (M0) that present viral antigen in the periphery (Figure 1) will classically activate these M0 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 M0, in amplifying adaptive immune responses, and in promoting tissue repair. However, if excessive or poorly resolving, then tissue injury may result from these M0 effector functions.

A dramatic example of the potential for bystander injury to the kidney by M0 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 M0 (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 be activated to perform localized effector functions that are dependent on perforin, granzymes, 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 restoration 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.

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Disclosures

None.

References

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