n a world where patients are exposed to countless prescription drugs, it is amazing that more humans do not develop autoimmune drug reactions that lead to tissue injury. Of course, the chance of drug-related inflammation rises in proportion to use, but it still seems most of us are comfortably protected from such events by the high activation threshold of our immune systems. Genetic polymorphisms that modulate the initiation of antigen-specific immune responses, particularly in the MHC, are a determining influence, but the whole story is more complicated.

Drugs in body fluids or their metabolites often form adducts (hapten + protein carrier) that modify their physical structures, occasionally making them immunogenic and prone to drug reactions (1). These adducts can be taken up by macrophages or dendritic cells and presented on the cell surface to attract the surveillance arm of the immune system. Sometimes a drug without a carrier also can interact directly with T cell receptors within the naive repertoire or be processed by antigen-presenting cells for potential simulation of new T cells. Some of these drug reactions are influenced by changes in metabolism induced by other drugs taken simultaneously; some are modified by the variability in local cytokine expression or the polymorphisms of enzymes that affect levels of metabolites, particularly cytochrome P-450; and in some cases, the inflammatory state depresses normal drug metabolism (2).

So, is the immune response and its attendant inflammation a result of primary toxic injury or the proximal inciting event? No one really knows for sure; it probably is a bit of both. The classic immune response produces a variety of antigen-reactive T cells, and the hapten-carrier effect is only one of several inciting mechanisms. T cells respond under the influence of MHC-restricted immune response genes and other genes that encode co-stimulation molecules (3,4). Of the many co-stimulation molecules, CD28/cytotoxic T lymphocyte antigen-4 (CTLA4) receptors and CD80/86 ligands seem particularly critical. Inducible CTLA4 expression suppresses early T cell responses, and a growing number of single-nucleotide polymorphisms near the CTLA4 gene now are linked to autoimmunity and tissue injury (3). The implication of these associations is that functional reductions in CTLA4 make some humans more susceptible to autoimmunity. Whether these CTLA4 effects can be linked to drug-induced hypersensitivity remains to be seen.

The concentrated presence of CD4\(^+\) helper T cells at the site of injury is a telltale sign of immune activation. Helper cells come in two varieties: Th1 helper cells (releasing TNF-\(\beta\) and \(\gamma\)-IFN) favor delayed-type hypersensitivity responses and the production of CD8\(^+\) cytotoxic lymphocytes, and Th2 cells (releasing IL-5 and IL-4) attract eosinophils and help B cells form plasma cells that secrete antibodies (5); CD4/CD127lo suppressor T cells can attenuate the activation of Th1 and Th2 lymphocytes (6). Immune responses that evade suppression often are a mixture of CD4\(^+\) and CD8\(^+\) lymphocytes. The sum of various populations of T and B cells confer the antigen-specific character of tissue inflammatory responses in situations such as interstitial nephritis (7,8). T lymphocytes and not antibodies ignite most forms of interstitial nephritis.

In the current issue of the JASN, Spanou et al. (9) report on the variability of immune responses in several patients who developed drug-induced interstitial nephritis. Whereas drug reactions classically are systemic, their manifestations typically are limited to tissues of the skin, liver, and kidneys. Why this is so is not entirely clear, but the liver is a major site of drug accumulation before metabolism, the kidneys filter many drugs that concentrate their exposure to tubular epithelium during passage, and the skin is a special source of photostimulation. Some of these sites probably achieve critical levels of drug accumulation that serve as a tissue source of antigen.

Spanou et al. remind us that although many details of the T cell response have been well worked out in mice with interstitial nephritis (10), it has been much harder to characterize the antigen-specific immune response in humans, even in those who receive pharmaceutical drugs. Nevertheless, drug hypersensitivity is one convenient window for showcasing the role of T cells in human interstitial nephritis. Each of the three patients reported in this study had antigen-specific and, possibly, oligoclonal proliferative T cell responses to a particular drug (9). The cytokine response of drug-reactive T cell clones from peripheral blood in these patients reflected both Th1 and Th2 responses, and some of the clones expressed CXCL8, a neutrophil that attracts chemokine, or IL-5, which attracts eosinophils. Although CD8\(^+\) lymphocytes were present in the interstitium in one of the reported renal biopsies, evidence of cytotoxicity was weak. Whether the T cell clones were truly oligoclonal cannot be determined without cDNA sequencing a good number of CDR3 regions that form part of the V\(\beta\) chain of their
antigen-specific T cell receptors (11,12). The CDR3 region of the Vβ chain is fashioned by VDJ recombination and an oligoclonal response should express only a limited number of recombination events.

Where does all of this leave us? The evidence that T cells are involved in drug-induced interstitial nephritis continues to be strong, and some features of the cells involved suggest mechanisms of additional pathophysiology, particularly as it relates to attraction of other inflammatory cells (1). Clinical empiricism dictates that stopping offending drugs is appropriate in patients with drug hypersensitivity and interstitial nephritis, and most patients fortunately will show signs of improvement in their urinalysis and renal function. More often than not, physicians also will start a short course of steroids, and a few will add cyclophosphamide if initial interventions are not successful (13). Our approach to this problem at the bedside has not advanced much in the past decade.

The future, of course, is exciting. Growing interest in pharmacogenomics and personalized medicine for predicting genetic polymorphisms in drug metabolism and immune activation, such as CTLA4, hold great promise for up-front selection of drug classes and interactions to be avoided in individual patients (14,15). Urine proteomic signatures and the advance of predictive biomarkers for inflammation also may allow us to adjust medication without having to resort to a renal biopsy (16,17). Deeper work on understanding the immunologic nature of human interstitial nephritis also would be welcome.

References

See the related article, “Involvement of Drug-Specific T Cells in Acute Drug-Induced Interstitial Nephritis,” on pages 2919–2927.