Declassifying Glomerulonephritis

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In the structured world of biomedical education, organ pathology is usually divided into neatly ordered categories. Such classification schemes, often based on current understanding of disease mechanisms, are rapidly accepted by those seeking order in seemingly chaotic disciplines. The field of glomerulonephritis, like other enigmatic disciplines, has lent itself to meticulous cataloging for more than 50 years. Terms such as immune versus nonimmune or toxic versus nontoxic glomerulonephritis abound in the literature, and further subclassification of immune glomerulonephritis into antibody-mediated versus T cell-mediated grace the titles of book chapters and review manuscripts. One is left wondering, however, whether these classification schemes are based on deep understanding of disease pathogenesis or merely reflect our ignorance of common biologic mechanisms that link seemingly disparate diseases.

In the current issue of JASN, Wu et al. provide new evidence that ostensibly different classes of glomerulonephritis share fundamental biological underpinnings, irrespective of the etiological agent that initiates glomerular injury (1). The authors report that infiltration of the kidney by the γδ T cell, a member of the so-called innate lymphocyte populations, is a feature common to both toxic (presumably nonimmune) and nontoxic (predominantly immune-mediated) glomerulonephritis. They demonstrate that γδ T cells accumulate in mouse kidneys after induction of toxic (adriamycin) nephropathy, just as they would in immune-mediated Heyman nephritis in rats or IgA nephropathy in humans (2,3). Importantly, these T cells serve a critical regulatory function that dampens interstitial inflammation and glomerulosclerosis. The manuscript by Wu et al. comes at the heels of several publications showing that αβ T cells (either CD8+ effector or CD4+CD25+ regulatory T cells) normally associated with immune-mediated glomerulonephritis are also central players in the pathogenesis of adriamycin nephropathy (4,5). So what then is the common pathogenetic thread that blurs the distinction between nontoxic (immune) and toxic (nonimmune) forms of renal injury?

The short answer is “innate immunity” or, more precisely, our ever-expanding view of what the immune system is and does. Traditionally, the term immunity had been restricted to classic adaptive immune responses; that is, antigen-specific reactions that trigger B and T cell activation and differentiation, antibody isotype switching, and the generation of immunological memory. On the other hand, inflammatory events that either precede or accompany classic adaptive immunity were summarily labeled as nonspecific and therefore nonimmune. The realization over the past 15 years or so that the early inflammatory response to microbial infection is in fact a specific response to pathogen-associated molecular patterns, that these microbial products are recognized by discreet pattern recognition receptors on inflammatory as well as noninflammatory cell populations, and that this early response is essential for triggering adaptive immunity has succeeded in reuniting inflammation and immunity (6). In short, the inflammatory system that triggers adaptive immunity gained the quality of specificity and took on the moniker of “innate immunity.” The function of the innate immune system is of course not restricted to sensing microbes but extends to detecting both nonmicrobial nonself (for example, transplanted organs [7]) and altered or stressed self as occurs in malignancy and inflammation (6), including conditions that affect the kidneys (8,9).

The finding by Wu et al. that γδ T cells are involved in adriamycin nephrotoxicity is therefore not a surprise as these cells are an important brigade in the army of cells that make up the innate immune system (10). Unlike traditional αβ T cells, γδ T cells have a much more restricted T cell receptor repertoire and interact with nonclassic major histocompatibility molecules. They reside in high numbers in epithelial tissues (e.g., the gut and skin), where they respond quickly to tissue-specific stress antigens. Although initially thought to play an essential role in mounting immunity against microbial infection, it has become evident that their principal function is to regulate local immune responses (10). In other words, they minimize tissue pathology by downregulating innate and adaptive immune responses. The observation by Wu et al. that adriamycin nephropathy is more severe in the absence of γδ T cells is consonant with this paradigm. γδ T cells, however, can also be proinflammatory. One relevant example is accelerated nephrotoxic serum nephritis, whereby genetic deletion of γδ T cells protected against proteinuria and glomerular macrophage accumulation (11). The reasons for the functional plasticity of γδ T cells remain to be explored.

Throughout evolution fundamental biological systems that are advantageous to the survival of the species are conserved
among animal phyla and, more importantly, co-opted to fulfill multiple functions in the same organism. Innate immunity is a prime example of such a valuable biological system. It is not only critical to recognize nonself, particularly microbial invaders, but is also essential to sense tissue damage and initiate the healing process. Therefore, as the distinctions between immunity and inflammation continue to blur, it is inevitable that rigid disease classification systems will begin to collapse. “De-classifying” glomerulonephritis is a welcome first step toward removing the shroud of secrecy that has for so long concealed common, fundamental, biological processes underlying glomerular injury and repair.

Disclosures
None.

References

See the related article, “Depletion of γδ T Cells Exacerbates Murine Adriamycin Nephropathy,” on pages 1180–1189.