Innate Immunity and Dendritic Cells in Kidney Disease and the Nobel Prize

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Published online ahead of print. Publication date available at www.jasn.org.

On December 10, 2011, the Nobel Prize for Physiology or Medicine will honor the work of Jules Hoffmann, Bruce Beutler, and Ralph Steinman for their landmark discoveries in the field of immunology. This recognition brings wide attention to a paradigm shift in understanding how multicellular organisms sense and interpret their external and internal environments in maintaining homeostasis or initiating host defense in case of pathogen danger and infection.1,2 Unraveling these fundamental processes not only allowed a better understanding of how pathology develops but also offered novel possibilities for disease prevention and cure, including kidney diseases.

It was the previous Nobel laureate, Christiane Nüsslein-Volhard, that unexpectedly set the stage for a piece of this year’s award. Nüsslein-Volhard had induced random mutagenesis in Drosophila to search for unknown genotype-phenotype associations. In 1984, one such mutant attracted her attention so much that she shouted the German word Toll, meaning “great.” Obviously, her joy encouraged her postdoctoral fellows to name the mutated gene as such. During the following decade, a few papers were published on the role of Toll for dorsal-ventral polarity of flies. This changed dramatically when Jules Hoffmann’s group in Strasbourg reported in 1996 that Toll-deficient flies succumb to fungal infection, which established a role for Toll in host defense.3 One year later, the Janeway Laboratory at Yale described the human homologue Toll-like receptor (TLR) genes.4 Unfortunately, Janeway died in 2003 and was no longer eligible to receive the prize.

The discoveries of Hoffmann and Janeway alerted immunologists all over the world to the possibility of a new signaling pathway, and in 1998, Bruce Beutler and colleagues at the Howard Hughes Medical Institute in Dallas first identified TLR4 as recognizing bacterial endotoxin.5 Beutler’s approach was as clever as simple. He took advantage of two well-known lipopolysaccharide-resistant mouse strains to map the newly discovered loci of the Toll genes. In doing so, he realized that endotoxin resistance was linked to loss-of-function mutations in the Tlr4 gene.

Two more circumstances encouraged researchers from many disciplines to rush into this new area of science, producing more than 18,000 related publications within the last 15 years: first, Tlr4 mutant mice as well as suitable immunostimulatory compounds, now discovered as agonists for distinct TLRs, became available at relatively low costs to everyone, and second, Shizou Akira, in Osaka, produced null mice for most TLRs and many other related genes, and did not hesitate to share them with collaborators and competitors. His generous attitude enormously pushed the field forward in short time.6 But what has this all to do with the kidney?

The kidney is a sterile organ but well equipped with TLRs and other innate pattern recognition receptors ready to signal danger upon the entry of pathogens. For example, in infective pyelonephritis, ascending uropathogenic *Escherichia coli* provide endotoxin from their bacterial wall to engage TLR4 on tubular epithelial cells and intrarenal dendritic cells, a process triggering the release of cytokines and chemokines leading to renal inflammation involving the rapid recruitment of neutrophils into the kidney and the tubular lumen noted on urinalysis. Tlr4 mutant mice cannot recognize bacterial endotoxin inside the kidney; hence, uropathogenic *E. coli* no longer induce chemokines and neutrophil recruitment.7 Insufficient immune recognition, however, is Janus-faced, and failing local pathogen control allows potentially fatal systemic spreading through immunodeficiency reminiscent of urosepsis. On the other hand, lack of TLR4 prevents immunopathology such as renal abscesses in *E. coli* pyelonephritis.

Meanwhile, it is clear that TLRs more than guard against pathogens as a potential source of danger in tissue homeostasis. Dying cells in that environment release intracellular factors with comparable potential to trigger local inflammation through TLRs.8 This means innate immunity not only signals pathogen entry but also monitors tissue integrity, which can be disrupted by any type of injury. Thus, renal cell necrosis involves additional immunopathology by activating innate immunity. Numerous studies now document that too much TLR signaling causes additional renal damage in acute kidney
injury and that blocking TLR signaling protects kidneys from inappropriate immunopathology. This amplification of injury not only involves TLRs; RIG-like helicases, the inflammasome, small leucine–rich proteoglycans, and lectin receptors add to the complexity of innate pattern recognition.

The other half of the 2011 Nobel Prize was awarded to the late Ralph Steinman, for his discovery of dendritic cells and their unique capacity to activate and regulate adaptive immunity. Dendritic cells are not immune effectors themselves; they instruct other immune cells, especially T lymphocytes. To this end, dendritic cells exist in virtually all tissues as immune sentinels. Once they sense pathogens using pattern receptors like TLR, they become activated and gather and carry suspicious antigenic material to lymph nodes to activate T lymphocytes, another immune cell type originally identified by Jacques Miller in the early 1960s. These T cells in turn become activated to perform various immune responses, such as cytotoxicity, delayed-type hypersensitivity, or stimulating B lymphocytes to produce antibodies.

Lymphocytes do not simply calm down after performing their immune engagement. Some of them persist as so-called memory cells, which are capable of faster, stronger, and more specific responses, such as when pathogens reinfect an organism. Such immunologic memory is the basis of all vaccinations and of immunity in its original meaning. After the Nobel committee in 1996 had honored the complicated mechanism by which T cells are activated by dendritic cells, so-called MHC restriction, this year’s prize pays tribute to the immune cells that engage this mechanism, and their discoverer.

Ralph Steinman discovered dendritic cells in 1973 as a postdoctoral fellow with Zanvil Cohn at the Rockefeller University. Dendritic cells are characterized by numerous branched projections, the dendrites from the Greek word, Dendron, meaning tree. He described these cells as motile, continuously extending, retracting, and reorienting their dendritic processes, but comparatively poor in endocytosis. Before the discovery of MHC restriction, this functionality appeared bewildering, and it took a long time to appreciate its exquisite suitability for T cell activation. Dendritic cells use small amounts of captured antigen extremely efficiently for T cell activation, taking advantage of unique intracellular mechanisms such as cross-presentation. In addition to antigens from pathogens, dendritic cells also present self-antigens. The latter antigens normally engage autoreactive T cells, which otherwise would lead to autoimmunity, but instead induces their apoptosis. In other words, dendritic cells (DCs) also maintain homeostasis by preventing autoimmunity; their failure to tolerize autoreactive T cells is a critical factor in autoimmunity. Thus, DCs can be considered the maestro of adaptive immunity.

DCs also heavily affect renal disease, although this was realized much later than in other disciplines, and consequently, the field of dendritic cells in the kidney has lagged somewhat behind. Initial descriptions of renal tubulointerstitial cells with morphologic characteristics of dendritic cells date back to the early 1990s, but studies of their functional roles were only initiated about 10 years ago. Since then, it has become clear that kidney dendritic cells act as sentinels against injury after renal obstruction or ischemia/reperfusion, in that they suppress unwanted intrarenal immune responses. However, in chronic kidney inflammation, they mature and drive progression of renal disease. Notably, they also orchestrate innate defenses against bacterial pyelonephritis by recruiting neutrophils into the kidney. The potential of kidney dendritic cells to affect renal inflammation makes them highly promising therapeutic candidates.

Only a few hours before the Nobel committee decided to award the prize to him, Ralph Steinman lost his long battle to cancer, a cancer that was treated successfully for 4 years using immunization protocols that depend on dendritic cell function. Although the Nobel Prize is not awarded posthumously, exceptions can be made, and the committee decided to do so in this special case. The president of the British Royal Society, Sir Paul Nurse—himself a Nobel laureate—commented: “This is a great tragedy. Ralph Steinman’s work was ahead of its time and he waited too long for the Nobel Prize. To die just days before its announcement is almost too much to bear. He will be remembered as one of the great immunologists of our time.” Jules Hoffman, Bruce Beutler, and Ralph Steinman were awarded the Nobel Prize 2011 because their discoveries advance our understanding of immunopathology. It remains our task to bring this to the benefit of patients with kidney disease.

ACKNOWLEDGMENTS

H.J.A. is supported by grants from the Deutsche Forschungsgemeinschaft (AN372/9-2, 10-1, 14-1, and GRK 1202). C.K. is supported by grants from the Deutsche Forschungsgemeinschaft (KFO228, SFB TR57, SFB704, SFB645) and by the EU Consortium Intricate.

DISCLOSURES

None.

REFERENCES

The discovery of the prorenin receptor, now nearly a decade ago, altered our view of the renin-angiotensin system (RAS). Binding of prorenin, the inactive precursor of renin, to the prorenin receptor results in full catalytic activity of prorenin through a nonproteolytic mechanism that likely involves a conformational change by which the prosegment moves out of the catalytic cleft, which then becomes available for the substrate, angiotensinogen. Binding of renin or prorenin (here together denoted as prorenin) to the prorenin receptor also activates intracellular signaling pathways in several cell models independent from angiotensin generation, which leads to increased cellular proliferation, cytoskeletal rearrangements, and the production of profibrotic and proinflammatory factors.

Plasma prorenin levels are approximately 10-fold higher than those of renin and increase even further under certain pathologic conditions, such as diabetes mellitus complicated by nephropathy. Hence, prorenin could be a source for renin activity resulting in tissue angiotensin generation and for angiotensin-independent signaling contributing to end-organ damage by mediating fibrosis and inflammation. However, studies using the putative prorenin receptor blocker, handle region peptide, in pathologic models have yielded conflicting results.

Recently, the focus has moved away from the RAS field and centered on other functions for the prorenin receptor, independent from prorenin. Different from other RAS genes, the prorenin receptor gene is an essential gene, and strategies to unravel the pathophysiological function of the prorenin receptor have therefore focused on using tissue-specific null alleles. Cardiomyocyte-specific prorenin receptor ablation results in early mortality due to heart failure. The cardiomyocytes of these null mice are characterized by extensive vacuolarization and impaired autophagic digestion because of decreased vacuolar-type H\(^+\)-ATPase (V-ATPase) activity. The carboxyterminal 8.9-kD fragment of the prorenin receptor co-purifies with the V-ATPase from bovine adrenal secretory vesicles and is therefore also referred to as ATP6AP2 (ATPase, H\(^+\)-transmembrane V0 pore domain that translocates protons)

The Prorenin Receptor: What’s in a Name

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doi: 10.1681/ASN.2011100981

Published online ahead of print. Publication date available at www.jasn.org.

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