Dangers Within: DAMP Responses to Damage and Cell Death in Kidney Disease

Diane L. Rosin*† and Mark D. Okusa†‡

Departments of ‡Medicine and *Pharmacology and the †Center for Immunity, Inflammation and Regenerative Medicine, University of Virginia, Charlottesville, Virginia

The inflammatory response to acute or chronic tissue injury engages the immune system. What are the initial activators of injury or disease? How does the immune system discriminate between live versus dead cells and know whether to respond? What factors regulate the inflammatory response to clear injury without causing excessive tissue damage and then initiate repair? We now recognize that the well-known activation of the immune system in response to foreign pathogens is recapitulated in an immune response to endogenous molecules released from necrotic, and perhaps apoptotic, cells after tissue injury or trauma related to hypoxia, ischemia, mechanical stress, or pathogen-induced inflammation.

Matzinger originally proposed the danger model to clarify exceptions to Janeway’s model of the immune response to foreign antigens, which did not at the time explain autoimmunity or the immune response to transplantation. The danger model suggests that damaged or dying cells release endogenous molecules called damage-associated molecular patterns (DAMPs) that activate cellular receptors leading to downstream inflammation. Thus endogenous danger signals and exogenous PAMPs elicit similar responses through seemingly similar mechanisms. Also emerging is our understanding that normal repair processes benefit from dampening the immune response to these endogenous danger molecules. Here we focus on the role of DAMPs and their putative receptors in the pathogenesis of acute and chronic kidney diseases.

ABSTRACT

The response to exogenous pathogens leads to activation of innate immunity through the release of pathogen-associated molecular patterns (PAMPs) and their binding to pattern recognition receptors. A classic example is septic shock where Toll receptor 4 recognizes PAMPs. Although well accepted, this concept does not explain the activation of innate immunity and inflammation occurs with transplantation, autoimmunity, or trauma. Increasingly recognized is that endogenous molecules released by dying cells (damage-associated molecular patterns; DAMPs) activate cellular receptors leading to downstream inflammation. Thus endogenous danger signals and exogenous PAMPs elicit similar responses through seemingly similar mechanisms. Also emerging is our understanding that normal repair processes benefit from dampening the immune response to these endogenous danger molecules. Here we focus on the role of DAMPs and their putative receptors in the pathogenesis of acute and chronic kidney diseases.

DANGER-ASSOCIATED MOLECULAR PATTERNS: ENDogenous DANGER SIGNALS

A consistent terminology has not been adopted for the endogenous molecules that convey a danger signal to the immune system. Some DAMPs that stimulate an immune response have been called adjuvant molecules to distinguish them from DAMPs that produce only acute pro-inflammatory effects, sometimes referred to as alarmins. PAMPs and alarmins have been grouped together as subcategories of a large family of DAMPs whereas others consider alarmins and DAMPs to be related molecules that are clearly distinguished from PAMPs. Here we use the term DAMPS to describe endogenous danger mole-
cules as a group that is separate from pathogen-derived PAMPs (Table 1 and Figure 1); their classification is predicated on direct evidence of involvement in the immune response to injury with a clear absence of confounding effects from potential bacterial contaminants, such as LPS.3,16

High-mobility Group Box 1 Protein

Perhaps the most well characterized DAMP, high-mobility group box 1 (HMGB1) protein, is a ubiquitously expressed nonhistone DNA-binding protein that regulates chromosomal stability, stabilizes nucleosomes, and regulates transcription.18–22 As an extracellular DAMP after secretion or passive release,23 HMGB1 is a late-phase pro-inflammatory mediator in sepsis24 and in sterile inflammation, such as hepatic ischemia-reperfusion injury (IRI).18,25 HMGB1 is chemotactic for immune cells and stimulates dendritic cell (DC) maturation and migration.26 HMGB1 binds to the receptor for advanced glycation end products (RAGE)27 and stimulates NFκB-induced transcription through interactions with TLR2, TLR4,28 and RAGE.

S100 Protein Family

The S100 proteins, a large family of calcium-binding proteins, are implicated in the inflammation or fibrosis associated with cancer or diseases of the kidney, heart, joints, and lungs.29 When functioning extracellularly as DAMPs after release from phagocytes30 and other cells in response to cell stress, S100 proteins bind to RAGE31 and other receptors and produce earlier pro-inflammatory effects like HMGB1.32,33 S100A8 and S100A9 release from activated phagocytes activates TLR4 and amplifies lethal endotoxin-induced shock.33

Other Ligands of RAGE

A diverse group of ligands (including HMGB1, S100 proteins, and HSPs) bind to RAGE. Advanced glycation end products (AGE) and related molecules are glycation and oxidation products of proteins and lipids that are formed in hyperglycemic states by oxidative stress, such as hypoxia and ischemia/reperfusion, and in a number of diseases.39–42

Genomic Double-stranded DNA

Microbial DNA is a ligand for TLR9, but TLR9 can also recognize self-DNA from injured mammalian cells.43 Release of DNA from dying mammalian cells initiates an innate immune response by activation of TLR9 and the NALP3 (cryopyrin) inflammasome, release of activated IL-1β and IL-18,44 and induction of DC maturation.45 In addition to genomic DNA, injury-induced release of mitochondrial DNA can also cause inflammation by conserved pathogenic PAMP sequences.46,47

Uric Acid

The accumulation of uric acid in tissues has long been known to cause gout, but soluble uric acid released by injured cells also acts as a danger signal.48 The active moiety, monosodium urate crystals, forms in the extracellular space where it stimulates an immune response by activating the NALP3 inflammasome49–52

Table 1. DAMPs and receptors for DAMPs

<table>
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<tr>
<th>DAMP</th>
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CXCRC2, CXC-chemokine receptor 2; FPRL1, formyl peptide receptor-like receptor 1; MSU, monosodium uric acid; NLRP3, NLR family, pyrin domain-containing 3.

Heat-shock Proteins

In normal healthy cells, heat-shock proteins (HSPs) are intracellular protein chaperones that guide newly synthesized polypeptide chains to prevent aggregation and misfolding. During cell stress, induction and secretion of HSPs causes pro-inflammatory cytokine and chemokine release and activation and maturation of antigen-presenting cells (APCs) to produce a robust innate immune response.34–36 Indeed, HSPs extend their role as chaperones intracellularly by binding and presenting antigens to cell surface MHC class I molecules.37,38 Complexes of extracellular HSPs and antigens are taken up by APCs and presented to MHC I to activate T cells through cross-presentation.36,37

DAMPs and Kidney Disease
and by stimulating DC maturation and T-cell responses.52

Neutrophil-derived Alarmins
Neutrophils, an early leukocyte to infiltrate tissue after injury or infection, undergo degranulation and release immune modulatory proteins and polypeptides. Neutrophil-derived alarmins (such as α-defensins,53 cathelicidin,54 and lactoferrin55), named for their response to dant protein in urine, but its function remains unclear; it is unknown whether different DAMPs have specific roles, whether specific functions are elicited in different cell types or conditions, or even whether immune responses to DAMPs can be distinguished from those of PAMPs.

Extracellular DAMPs
Damaged or dying cells can also generate danger signals by cleaving molecules that are structural components of the ECM. Cleaved ECM glycoproteins, such as fibronectin and fibrinogen, and proteoglycans, such as hyaluronan, biglycan, and versican, function as DAMPs by signaling through TLRs, the NLRP3 inflammasome, and other receptors such as CD44, promoting a vigorous immune response5,6 and contributing to kidney disease.57

Other DAMPs
Other candidate DAMPs include galec-tins58,59, ATP and adenosine60–62, thioredoxin, a ubiquitous antioxidant enzyme63,64; the intranuclear cytokine, IL-3365; and Tamm-Horsfall protein (THP; or uromodulin), a glycoprotein expressed in the thick ascending limb that is excreted into the urine after proteolytic cleavage. THP is the most abundant protein in urine, but its function remains unclear; it has been implicated as a biomarker of kidney disease and allograft rejection66,70 and may be a damage signal in renal tubular injury. THP promotes cytokine release71 and immune cell activation, including DC maturation,72 but may also have a protective anti-inflammatory role.73

RECEPTORS
DAMPs are recognized by pattern-recognition receptors such as certain TLRs, NOD-like receptors (NLRs, including the NLRP inflammasomes), and RLRs (RIG-I-like receptors), thereby overlapping with PAMPs,74,75 and by specialized receptors such as RAGE.76 Common signaling pathways shared by DAMPs and PAMPs may have an evolutionary basis.77 Injury-induced release of bacterial-related DAMPs from mitochondria, evolutionary symbiotic descendents of bacteria, causes inflammation.46 Other DAMPs receptors include CD91, scavenger receptors, CD2, integrins, chemokine receptors, and CD44,3,11,16,74

RAGE is a multiligand receptor that binds AGE, some S100 proteins, amyloid protein, and HMGB1. It amplifies immune responses39 and is implicated in diseases such as diabetes, Alzheimer’s disease, cancer, and various inflammatory conditions.40,76,77 A soluble form of RAGE (sRAGE) found in human and mouse plasma78 may act as a ligand decoy to bind danger molecules and check the immune response. Circulating sRAGE and a splice variant (endogenous secretory RAGE) may be clinical indicators or biomarkers for the severity of disease.41,79

Inflammasomes, large cytosolic complexes of NOD-like receptors, adaptor protein, and caspase-1, link pathogenic and endogenous danger signals to activation of caspase-1, and proteolytic processing and release of the proinflammatory cytokines, IL-1β, and IL-18,50,80,81 Inflammasomes are important in gout,82 and their role in disease has been linked to several DAMPs, including the ECM molecule, biglycan.57

CHECKS AND BALANCES
With such a vast array of stranger and danger signals and some crossover in

![Figure 1. Danger and stranger models. Infections of pathogenic bacteria or viruses cause release of PAMPs that bind to pattern recognition receptors (PRRs), such as TLRs, on immune cells and stimulate an innate immune response that is accompanied by inflammation, activation of adaptive immunity, and eventually processes to resolve the infection and allow for tissue repair. The danger model recognizes that similar events occur when cells are stressed or injured and that necrotic cells release molecules that are normally hidden within the cell. In the extracellular space these DAMPs can bind to PRRs or to specialized DAMP receptors to elicit an immune response by promoting release of pro-inflammatory mediators and recruiting immune cells to infiltrate the tissue. The immune cells that participate in these processes include, for example, APC, such as dendritic cells and macrophages, as well as T cells and neutrophils (PMN). DAMPs may also stimulate adaptive immunity and participate in autoimmune responses and tissue repair. A wide variety of intracellular and extracellular molecules function as DAMPs when released from cells (Table 1). The functions of such a diverse group of molecules may not yet be fully elucidated; it is unknown whether different DAMPs have specific roles, whether specific functions are elicited in different cell types or conditions, or even whether immune responses to DAMPs can be distinguished from those of PAMPs.](http://www.jasn.org)
their receptors, how does the immune system distinguish PAMPs from DAMPs? Furthermore, once an immune response is initiated, what mechanisms are engaged to prevent rampant tissue damage and begin the repair process? Although PAMPs and DAMPs bind to some of the same receptors, interaction with different coreceptors may account for a divergence in downstream effects allowing for discrimination between PAMPs and DAMPs and selective suppression of DAMP signaling (Figure 2).85–87

Some mechanisms control damage-inducing immune responses through DAMPs inactivation. Anti-HMGB1 antibodies and sRAGE reduce HMGB1 bioavailability.40 Extracellular exosomal conditions may regulate the immune response by balancing early-stage reducing environment-promoting pro-inflammatory conditions with late-stage oxidation-induced DAMPs inactivation; disruption of this balance may contribute to chronic inflammation.19,89,90 BCL2 proteins, a family of pro- or antiapoptotic moieties, may be tissue protective when released extracellularly in IRI.91

Some endogenous molecules contribute to the resolution of inflammation and initiation of renal repair.92 Weibel-Palade bodies are organelles of endothelial cells that contain bioactive substances such as von Willebrand factor, IL-8, P-selectin, angiopeptin-2, and eotaxin93 that participate in hemostasis and inflammation. Uric acid release after IR mobilizes stem cells, protects kidneys from injury,94,95 and through exocytosis of Weibel-Palade bodies and release of their constituent molecules may promote postischemic repair.96 Some DAMPs, including HMGB1 and some ECM proteins, such as hyaluronan and heparin sulfate, initiate immune responses but are also necessary for recovery and healing.19

DAMPS AND KIDNEY DISEASE

Despite significant advances in understanding the important contribution of inflammation and immune mechanisms to the pathogenesis of a variety of kidney diseases, few specific or efficacious therapies exist. Understanding the role of candidate DAMPs released from somatic kidney or immune cells could reveal novel drug targets for inhibiting the inflammatory response or promoting repair processes in acute and chronic kidney disease (CKD). DAMPs contribute to multiple diseases. TLRs are important in IRI and various forms of glomerulonephritis including lupus nephritis.12–15 Advanced glycation end products, DAMPs that bind to RAGE rather than TLRs, are increased in renal failure and are involved in the progression of CKD in diabetic and nondiabetic kidney disease.97,98

Acute Kidney Injury

Acute kidney injury (AKI) results most commonly from IR, and although there are many causes, a common pathway leading to proximal tubule injury is activation of innate and adaptive immunity leading to inflammation.99 Injury elicits release of pro-inflammatory DAMPs,
which may be signals that engender the inflammatory response to IRI by binding to receptors such as TLRs and RAGE.\textsuperscript{100} The best-characterized DAMPs in AKI are HSPs and HMGB1. Although their role in mediating renal injury in acute ischemic events is well documented, some studies do not establish that they function as DAMPs to stimulate the immune system. Nevertheless, we include them as viable DAMPs candidates on the basis of their role as DAMPs in other pathologies. In ischemic kidneys or hypoxic renal epithelial cells, stimulation of the TLR2-mediated ERK pathway is regulated by the HSP, gp96.\textsuperscript{101} Geldanamycin, an inhibitor of Hsp90 and gp96, protects mouse kidneys from IRI.\textsuperscript{102} Hsp70 and Hsp27 are up-regulated in rat kidneys after IRI\textsuperscript{100}; however, tissue-protective\textsuperscript{104} and pro-inflammatory\textsuperscript{105} roles for Hsp27 have also been reported in kidneys after IRI. Ethyl pyruvate, an inhibitor of HMGBl release, protects kidneys from IRI and reduces the increase in TNFα in rat kidneys subjected to IRI.\textsuperscript{106} TLR4- and MyD88-deficient mice showed protection from kidney injury; HMGBl, hyaluronan, and biglycan expression increased in these null mice, suggesting that these DAMPs may be ligands for the observed role of TLR4 in IRI.\textsuperscript{107}

High concentrations of uric acid accumulate in ischemic tissues and precipitate to form monosodium urate crystals that elicit an immune response. However, a single treatment with uric acid or the enzyme uricase to produce an acute rise in blood levels of uric acid mobilized endothelial progenitor cells and protected kidneys from IRI; this effect was absent with hyperuricemia.\textsuperscript{93} Kidney injury molecule-1 (Kim-1/Tim-1), one of a growing list of biomarkers of AKI and CKD, is a multifunction receptor protein expressed in proximal tubules that is released into the urine of patients with kidney disease.\textsuperscript{108} In addition to imparting phagocytic properties to tubule epithelial cells,\textsuperscript{109} Kim-1/Tim-1 may inhibit development of autoimmune responses and promote resolution of inflammation after kidney injury,\textsuperscript{108} therefore suggesting its role as a possible DAMP molecule or receptor.

**Diabetic Nephropathy and Nondiabetic Glomerular Diseases**

There is expansive literature on the involvement of AGE and RAGE in podocytes, diabetes, and diabetic nephropathy.\textsuperscript{42,76,97,110–117} It is presumed but not always demonstrated that these molecules are important as DAMPs because of the involvement of inflammation and the immune system in diabetes.\textsuperscript{42,115,118–120} RAGE, functioning as an endothelial adhesion receptor, is implicated in a novel pathway for leukocyte recruitment in inflammatory disorders and diabetic mice, and this process is enhanced by S100, a proinflammatory RAGE ligand.\textsuperscript{121} Experiments using RAGE null or overexpressing mice, neutralizing RAGE antibodies, or sRAGE implicate RAGE in the pathophysiology of diabetic nephropathy and chronic inflammation.\textsuperscript{76,112,122} In db/db mice, increased RAGE and s100 expression in podocytes associates with renal pathology and with increased infiltration of mononuclear phagocytes to glomeruli; these effects are blocked by anti-RAGE antibody.\textsuperscript{112} Serum RAGE levels, kidney damage, and inflammatory mediators in diabetic animals and humans are inversely related to levels of AGE receptor-1,\textsuperscript{123,124} suggesting an anti-inflammatory protective role for AGE receptor-1 in diabetes.\textsuperscript{123}

AGE, RAGE,\textsuperscript{97,117} and other DAMPs are also strongly implicated in the pathogenesis of nondiabetic glomerular diseases. Podocyte injury and adriamycin-induced glomerulosclerosis is accompanied by production of RAGE ligands; RAGE-deficient or sRAGE-treated mice are protected from glomerular injury.\textsuperscript{125} Increased AGE and RAGE levels, macrophage infiltration, fibrosis, and inflammation are found in the kidneys of mice that develop glomerular disease from an atherogenic high-fat diet; this lipid-induced renal injury is regulated in part by galectin-3.\textsuperscript{126} TLR4 is up-regulated in mouse models of cryoglobulinemic membranoproliferative glomerulonephritis and localizes to podocytes of nephritic glomeruli; stimulation of podocytes with either TLR4 ligands or fibrinogen results in similar patterns of enhanced chemokine expression, suggesting that TLR4 functions as a DAMP receptor for endogenous ligands and may mediate glomerular injury by stimulating innate immunity.\textsuperscript{127} In nephrotoxic nephritis, a model of rapidly progressive glomerulonephritis, Hsp60 is released from kidneys and excreted in urine, and administration of Hsp60 exacerbates disease in a T cell-dependent manner.\textsuperscript{128}

Expression of S100 proteins increases in kidneys in anti-Thy-1 antibody-induced glomerulonephritis, a rat model of mesangial proliferative glomerulonephritis.\textsuperscript{129} Patients with glomerulonephritis have HMGB1 in serum, interstitial mononuclear cells, and glomeruli.\textsuperscript{130} Two S100 proteins, myeloid-related proteins MRP8 and MRP14, are detected in macrophages in renal biopsies from patients with glomerulonephritis; the presence of these proteins and their heterodimeric complexes in macrophages infiltrating glomeruli correlates with the severity of the acute inflammatory process, and chronic inflammation associates with MRP8/14 infiltrates without complex formation in the renal interstitium.\textsuperscript{131}

**Fibrosis**

Expression of Hsp27, phospho-Hsp27,\textsuperscript{132} RAGE,\textsuperscript{133} and calreticulin\textsuperscript{134} is up-regulated in an animal model of tubulointerstitial fibrosis (unilateral ureteral obstruction [UUO]) and TGFβ-induced epithelial-to-mesenchymal transition in proximal tubular epithelial cells in vitro. The ECM protein, biglycan, increases in tubule epithelial cells 4 days after UUO and later in infiltrating and interstitial cells.\textsuperscript{135} Biglycan is a pro-inflammatory DAMP in UUO-induced kidney injury; activation of the NLRP3 inflammasome and increases in levels of pro-inflammatory IL-1β after UUO are reduced in biglycan null mice.\textsuperscript{57} Reactive oxygen species, oxidative stress, S100A4, and Hsp47 are involved in fibrosis after IRI, but their role in immune function has not been investigated.\textsuperscript{136}
Lupus Nephropathy and Autoimmune Disease
HMGB1 has been linked to the pathogenesis of a variety of proinflammatory and autoimmune diseases, including systemic lupus erythematosus (SLE). Circulating HMGB1 levels increase in SLE patients and in mice, and HMGB1 may be involved in antibody-induced kidney damage in SLE. In lupus-prone MRL-Fas(lpr) mice, p38 MAPK activation-induced infiltration and maturation of DCs and secretion of HMGB1 from DCs have been implicated in autoimmune kidney disease. Inflammatory and immune responses in SLE, and particularly in lupus nephritis, can be induced by HMGB1-nucleosome complexes, but necrotic nucleosomes also contain double-stranded DNA, which has long been recognized as a key mediator of lupus nephritis. Chromatin fragments can participate in the pathogenesis of kidney disease in SLE by stimulating the innate immune system and by engaging the adaptive immune response to produce antichromatin and anti-double-stranded DNA antibodies leading to glomerular deposits of immune complexes, which are the hallmark and likely the critical initiating events in lupus nephritis.

Transplantation
The contribution of DAMPs to IRI is likely also pertinent in kidney transplantation, because donor kidneys are susceptible to delayed graft function resulting from ischemia followed by reperfusion. Release of DAMPs, such as HMGB1, ATP, uric acid, and IL-1α, from allografts may induce pro-inflammatory effects and adaptive immune responses. TLRs mediate the effects of some of these endogenous molecules in transplant by signaling through type 1 interferons. In human kidney transplants, increased expression of TLR4 and HMGB1 is found in deceased donor kidneys, and kidneys from patients with a TLR4 loss-of-function mutation have lower levels of inflammatory markers and improved graft function post-transplant. Moreover, TLRs and their endogenous ligands may be important in chronic allograft dysfunction. Expression of DAMPs, including biglycan, HMGB1, and HMGB1, increases in the acute and chronic phases after kidney transplantation. Kidney transplants to mice lacking TLR2, TLR4, or the adaptor proteins, MyD88 and TRIF, show improved graft function and morphology and decreased leukocyte infiltration and expression of fibrotic markers, cytokines, and chemokines.

Higher levels of S100A8 and S100A9 in renal biopsies taken in the acute phase after transplant are predictive of favorable graft outcome (patients that later had stable graft function compared with those progressing to chronic allograft nephropathy). These S100 proteins are typically pro-inflammatory, but their beneficial role in wound repair may predominate in transplantation and rejection. Glycosylation of Tamm-Horsfall glycoprotein is altered, and its various immunomodulatory functions are diminished in renal transplant patients at least in part because of altered NF-κB p52 nuclear translocation.

Nondiabetic Chronic Kidney Disease
Many of the DAMPs molecules associated with AKI are also important in CKD. Increased HMGB1 levels correlate with pro-inflammatory markers and declining kidney function in CKD. Endothelial dysfunction in CKD, which associates with elevated serum levels of AGE, may be due to AGE-induced suppression of endothelial NOS. RAGE is proinflammatory in hemodialysis patients; sRAGE and endogenous secretory RAGE levels inversely correlate with renal function and inflammatory state in hemodialysis patients. Elevated TLR2 expression in patients with CKD and in mice with obstructive nephropathy associates with inflammation and increased expression of biglycan and HMGB1, but TLR2 may not be necessary for chronic kidney injury. By contrast Tamm-Horsfall protein activates innate and adaptive immunity through TLR4 and may play an inflammatory role in progression of CKD.

CONCLUSIONS
Processes that contribute to the pathogenesis of acute and chronic kidney disease involve the activation of innate and adaptive immunity. Release of endogenous molecules from dying cells leads to activation of innate immunity and downstream inflammation. By bridging to adaptive immunity, DAMPs also contribute to progressive injury or to attenuation of injury. As our understanding of these molecules and pathways evolves, information on precise therapeutic targets will likely lead to improved outcomes.

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