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# Dendritic Cells and Damage-Associated Molecular Patterns: Endogenous Danger Signals Linking Innate and Adaptive Immunity

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**Key Words**
Dendritic cells · Sterile inflammation · Damage-associated molecular pattern · Toll-like receptors · High mobility group box protein 1

**Abstract**
Dendritic cells (DCs) are potent antigen-presenting cells critical in regulating the adaptive immune response. The role of DCs is dichotomous; they may both present antigens and the appropriate stimulatory molecules to initiate an adaptive immune response, or they may induce tolerance and release anti-inflammatory signals. The activation of immature DCs, required for the expression of the necessary costimulatory T cell molecules, is dependent on pattern recognition receptors. In addition to the pathogen-derived ligands of pattern recognition receptors, several damage-associated molecular patterns (DAMPs) have recently been shown to interact with DCs and dramatically affect their ultimate function. The complex interplay of DAMPs on DCs is clinically important, with implications for transplantation, tumor immunity, autoimmunity, chronic inflammation and other conditions of sterile inflammation such as ischemia reperfusion injury. In this review, we will focus on the role of DAMPs in DC function.


## Dendritic Cells: The Basics

Dendritic cells (DCs) are the most potent antigen-presenting cells (APCs) functioning both as 'sentinels' by constitutively capturing antigens, and also as key orchestrators of the immune response, capable of both initiating an acquired immune response or inducing tolerance. The activation of innate immune cells is fundamental to the development of effective adaptive immunity. DCs are responsible for linking innate and adaptive immunity via the recognition and presentation of antigens to several cell types including CD4+ helper T cells, CD8+ cytotoxic T lymphocytes and B cells, among others [1]. Upon activation, DCs undergo a process called maturation; here they lose their phagocytizing ability and upregulate the surface expression of MHC class I and class II peptide complexes, upregulate the expression of costimulatory molecules (CD40, CD54, CD80 and CD86) and secrete proinflammatory cytokines. The mature DC also upregulates chemokine receptors enabling migration into draining lymph nodes. All these phenotypic changes in mature DCs allow them to be in close proximity to naïve T cells and express the requisite costimulatory molecules, priming the T-cell-mediated immune response [2]. Traditionally, it was thought that mature DCs initiate an im-

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mune response by stimulating lymphocyte subsets and immature DCs induce tolerance with their lack of the necessary costimulatory molecules for lymphocyte activation; however, it is now known that some mature DCs may also induce tolerance.

DCs are a heterogeneous population of cells with their characteristics depending in part on their origin and location within the body. They may be located either in lymphoid or nonlymphoid organs or found migrating in the blood stream. The two main categories are conventional DCs (cDCs) and plasmacytoid DCs (pDCs). cDCs display all the classic phenotypical and functional characteristics that were originally attributed to DCs [3]. pDCs, on the other hand, are unique in that they must be induced by inflammatory stimuli to display the typical DC characteristics. Their primary role is the release of type I interferons with their role in T cell priming being more ambiguous [4, 5].

The activation of DCs is induced by the binding of germline-encoded pattern recognition receptors (PRRs) to their respective ligands. Toll-like receptors (TLRs) are the best-characterized PRRs. In both mice and humans, pDCs express primarily TLR7 and TLR9, endosomal nucleic acid-sensing TLRs. cDCs, on the other hand, have less restricted TLR expression and express most TLRs, with the exception of TLR7 and TLR9 in humans [3].

The ligands of PRRs may be exogenously derived or pathogen-associated molecular patterns (PAMPs; e.g. LPS) or endogenously derived molecules, referred to as damage-associated molecular patterns [DAMPs; e.g. high mobility group box protein 1 (HMGB1)] [6]. The activation of TLRs on DCs subsequently activates intracellular signaling pathways through NF-κB, mitogen-activated protein kinases (MAPK) and interferon regulatory factor 3 (IRF-3). TLR engagement on cDCs modulates a myriad of cellular activities including decreased antigen endocytosis, more efficient antigen processing and presentation, cytoskeleton rearrangements and the migration to secondary lymphoid organs, the release of inflammatory cytokines and the expression of costimulatory molecules. These processes lead to DC maturation, reprogramming to promote the appropriate activation and differentiation of lymphocytes bearing clonally distributed antigen-specific receptors, initiating an adaptive immune response [3]. However, the response of DCs to TLR ligands is complicated by dependency on the timing of exposure. For example, when DCs are exposed to TLRs early during their differentiation there is inhibition of further differentiation and the development of tolerogenic properties [7, 8]. In addition to the role of DCs in propagating an adaptive immune response, mature DCs also stimulate other innate immune cells such as NK cells and NKT cells.

## Autophagy and Antigen Presentation

Traditionally, it was thought that endogenous antigens are processed by the proteasome and loaded onto MHC class I molecules in the endoplasmic reticulum, and exogenous antigens are taken up by phagocytosis and processed for MHC class II presentation in the lysosome. However, since the discovery of DCs in the early 1970s by Steinman, our knowledge of cellular biology has greatly advanced. We now know that there are many exceptions to these rules, with autophagy playing a major role in not only the loading of MHC class I for cross presentation, but also during the loading of exogenous ligands onto MHC class II molecules [9].

Autophagy is a highly conserved catabolic process that involves the degradation of intracellular components, such as proteins and organelles. It allows for cellular homeostasis during times of stress and starvation and plays a role in cellular defense [10]. The role of autophagy in antigen presentation has recently been described, and much work is still ongoing in this area of study. It is a constitutive process in professional APCs, as well as an essential part of antigen processing and loading in MHC class II loading compartments, to which autophagosomes frequently fuse [11–13]. While these studies provided initial evidence of the role of autophagy in DC function, additional evidence of its role in antigen presentation was provided by Jagannath et al. [14], who found that augmentation of autophagy in DCs enhanced the efficacy of the Bacille Calmette-Guérin (BCG) vaccination against tuberculosis (further supporting a critical role for autophagy in DC function). They demonstrated that the autophagy-inducing agent rapamycin enhanced antigen presentation on DCs, while attenuation of autophagy with the pharmacological inhibition or siRNA against Beclin-1 had the opposite effect and abrogated antigen presentation. Similarly, knockdown of another key autophagy protein, Atg5, impairs the processing of (1) extracellular antigens and MHC class II presentation to CD4+ T cells in vivo and (2) phagocytized antigens, by interfering with phagosome-to-lysome fusion and the delivery of lysosomal proteases to the phagosome [15]. In addition, some infectious agents are provided a survival advantage by their ability to interfere with autophagic

signaling in DCs. The HIV-1 virus is able to evade early immune control by DCs by inducing a rapid shutdown of autophagy. This process is dependent on the ability of the virus to activate mTOR, thereby inhibiting autophagy [16, 17].

The regulation of autophagic signaling in DCs is dependent on several upstream signals, most important of which are the TLRs and their ligands. Both PAMPs and DAMPs, functioning as TLR ligands, have been shown to stimulate autophagy in macrophages and DCs [18–20]. TLRs mediate autophagy through the interaction of their adaptor proteins, MyD88 and Trif, with Beclin-1 and Bcl-2. The binding of MyD88 and Trif leads to reduced binding of Beclin-1 to Bcl-2, subsequently increasing autophagy [21]. TLR signaling enhances the autophagy-dependent display of peptides on MHC class II molecules [22]. It has been demonstrated that when autophagy is induced in macrophages and DCs with either LPS or rapamycin, there is an enhanced presentation of antigens on MHC class II molecules [13]. In addition to promoting antigen presentation, TLR ligands can also signal the recruitment of autophagy-associated proteins (including LC3 and Beclin-1) to conventional phagosomes, increasing the maturation and destructive capacity of phagosomes [23]. This points to the regulation of autophagic signaling being a critical downstream function of TLR signaling in DCs.

### Damage-Associated Molecular Patterns

In the danger model proposed by Matzinger, 'danger signals' or molecules that are capable of activating PRRs can arise from an endogenous source, either by passive release from necrotic cells or actively from cells under stress [24–27]. Several endogenously released molecules, or DAMPs, function as important mediators of sterile inflammation. DAMPs derived from cellular injury or necrosis may provide a signal to DCs that an immune response is required to restore homeostasis. The prototypical DAMP is HMGB1. However, several other molecules have characteristics of DAMPs, such as heat shock proteins (HSPs), nucleic acids, S100 molecules, hyaluronan and uric acid among others [27]. We will focus our discussion on the role of DAMPs as mediators of DC function.

### High Mobility Group Box Protein 1

HMGB1 is a ubiquitously expressed nuclear protein that serves as a DNA-binding protein. While this protein is critical for normal cellular function, it also displays proinflammatory cytokine activity when released into the extracellular space [28–30]. In the setting of acute tissue injury, HMGB1 may be passively released from necrotic cells. Additionally, in several cell types, including immune and nonimmune cells alike, HMGB1 is actively secreted in response to several cellular stresses to provide a 'danger signal' to surrounding cells and tissues. Importantly, HMGB1 has been found to function as an inducer of autophagy [20, 31]. Whether HMGB1 is oxidized or reduced seems to influence its function, with the reduced form of exogenous HMGB1 increasing autophagy and oxidized HMGB1 increasing apoptosis [32–34]. HMBG1's role in autophagic regulation is likely mediated through the receptor for advanced glycation end products (RAGE) [35]. In addition to its role in autophagy, HMGB1 impacts the function of both cDCs and pDCs in numerous ways.

*Conventional DCs*

The maturation of DCs is a key step that transforms them into mobile APCs capable of coordinating a subsequent adaptive immune response. While several factors impact the maturation of DCs, HMGB1 is required for this process in cDCs by upregulating a number of costimulatory molecules, including CD83, CD54, CD80, CD40, CD58 and MHC class II molecules [28, 36, 37]. HMGB1 also acts to increase proinflammatory cytokine secretion and polarize a Th1 T cell response. Additionally, anti-HMGB1 antibodies abrogate DC migration in response to the CCR7 ligand CCL19 and CXCR4 ligand CXCL12 in vitro [37, 38]. Interestingly, while DCs likely encounter HMGB1 from surrounding necrotic or damaged cells, the autocrine/paracrine release of HMGB1 from DCs is a critical step in activated DC migration [39, 40]. Furthermore, the surface expression of RAGE, a major HMGB1 receptor, is required for HMGB1-mediated DC migration in vivo [41]. HMGB1 also modulates the function of other PRRs, including TLR4 and TLR9 in DCs. For example, HMGB1 increases the expression of TLR4 in hepatic DCs and enhances the secretion of TNF-α and IL-6 [42]. HMGB1 also enhances the immunogenicity of the TLR9 agonist CpG-ODN by directly binding to it and delivering it to intracellular, TLR9-containing endosomes. Furthermore, it also binds TLR9 intracellularly and hastens its delivery to early endosomes resulting in increased expression of IL-6, IL-12 and TNF-α [43].

Thus HMGB1 is a critical mediator of both cDC activation and migration, and serves to fine-tune the immune response to invading pathogens or to tissue damage.

*Plasmacytoid DCs*

HMGB1 also affects pDCS, which are thought to be the primary IFN-α-producing cells in the body. Although original reports were conflicting regarding the effect of HMGB1 on pDC activation [44, 45], recent evidence suggests a complex relationship between HMGB1 and other immune-modifying agents in activating pDCs [46]. HMGB1 and its receptor RAGE are necessary for TLR9 activation and IFN-α production by pDCs in a mechanism dependent on combining with DNA-containing immune complexes. Similarly, data from Urbonaviciute et al. [47] showed IFN-α production by pDCs was dependent on immune complex formation, but suggested that the process was independent of HMGB1 and RAGE. Thus the role of HMGB1 in modulating the responses of pDCs is not fully delineated and future studies will continue to investigate its role on this important DC subset.

## Heat Shock Proteins

HSPs are traditionally regarded as chaperone proteins that aid in protein translation and folding. Extracellular HSPs are regarded as DAMPs [48] and also influence the function of DCs. The HSP gp96 induces upregulation of MHC class II and the costimulatory molecule B7–2 along with activation of NF-κB [49, 50] in bone-marrow-derived DCs and pDCs, although its overall contribution to DC function remains controversial. While it promotes cDC activation, De Filippo et al. [50] suggest that gp96 engagement by pDCs may serve an anti-inflammatory role. Another HSP, HSP70, also affects DC function. It is a chemoattractant for DCs and promotes DC maturation [51] via TLR4 signaling [52]. HSP60 also induces the maturation of DCs [53]. Thus, HSPs are DAMPs that are critical for DC function and maturation.

## Nucleosomes and DNA

Nucleosomes are nuclear constituents consisting of histone proteins and DNA. Extracellular nucleosomes, released from necrotic or apoptotic cells, have been implicated in a number of disease states including systemic lupus erythematosus [47]. Nucleosome levels are elevated after acute injury [54, 55], malignancy [56] and in autoimmune diseases [47]. While the mechanisms governing the release and persistence of nucleosomes in the extracellular space are unclear, a number of mechanisms likely contribute to their presence. Nucleosomes, like other DAMPs, may be passively released from necrotic cells following acute, unscheduled cellular death. Late apoptotic cells also release nucleosomes [47]; this suggests a more orderly, planned release of these molecules. Like other endogenous molecules, nucleosomes and self-DNA modulate DC function.

Nucleosomes have the potential to directly stimulate DCs and promote their maturation and cytokine secretion [57]. Nucleosomes derived from late apoptotic cells that contain HMGB1 activate myeloid-derived DCs [47]. Other studies have focused on the contribution of nucleosome immune complexes in activating DCs. Chromatin immune complexes, but not non-specific protein immune complexes, activate bone marrow DCs via FcγRIII and TLR9 [58]. So, it appears as though nucleosomes contain specific immunogenic properties; however, it is unclear if they directly act on DCs or if their effects depend on their combination with other circulating serum factors.

Endogenous DNA is increasingly recognized as a circulating DAMP and contributes to inflammation associated with sterile inflammatory insults. Necrotic hepatocyte DNA is thought to contribute to warm hepatic ischemia reperfusion (IR) injury [59], and circulating mitochondrial DNA promotes inflammation in trauma [60]. Endogenous DNA is capable of activating DCs in both TLR9-dependent and independent fashions [61, 62] and thus has the potential to drive the inflammatory response through DC activation. Endogenous DNA is also recognized by pDCs, and this effect is dependent on coupling with the antimicrobial peptide LL37. The DNA/LL37 complex is a potent activator of pDCs and this interaction is hypothesized to drive autoimmunity under certain conditions [63].

The relationship between DAMPs and DC function is certainly complex and disparate effects may be observed in different organs. For example, certain DC populations in the liver are thought to be tolerogenic, limiting the inflammatory response to portal circulation-derived pathogens [64]. Isolated hepatic DCs display unique properties, secrete large amounts of the cytokine IL-10, and promote a Th2 response [65]. In warm hepatic IR it appears that cDCs, activated by host DNA, reduce inflammation and damage by secreting large amounts of IL-10 [66]. Thus, while the recognition of circulating DAMPs tends to activate DCs, thereby initiating an im-

mune response, this effect is not generalizable and is dependent on several factors, including organ specificity and DC subtype.

### Clinical Implications of Sterile Inflammation and DC Response

DCs play decisive roles in a host of disease processes, including the immune response to malignancy [67–69], autoimmune diseases such as systemic lupus erythematosus [46, 47], IR [42, 66] and transplantation [70–72]. The substantial influence that DAMPs have on the function of DCs has important clinical implications in these disease processes. The possibility to alter either their exposure to danger signals or ligand binding to PRRs and subsequent signaling cascades are promising therapeutic targets. Although it is likely that the DAMP effect on DCs in coordinating the transition of sterile inflammation to an adaptive immune response is applicable to a multitude of clinical settings, the disease processes that currently have the clearest link from the available literature are malignancy and IR injury. Therefore, we will focus our attention on malignancy and IR to illustrate the connection of DAMPs on DC function in the clinical setting.

#### Role in Malignancy

DCs play a critical role in the body's response to tumor development and progression. A successful antitumor response relies on DCs to effectively capture, process and present tumor antigens to antigen-specific CD4+ Th1 cells, which in turn promote the recruitment of tumor-specific CD8+ cytotoxic T lymphocytes. The activation of DCs in response to DAMPs released from tumors may allow for the generation of an effective adaptive immune response against the neoplasm. DAMP-induced autophagy plays a major role in MHC class I cross presentation of tumor antigens and also MHC class II loading [73, 74]. However, tumors may also induce unresponsiveness in DCs, possibly leading to tolerance [75]. Increased numbers of pDCs found within tumor tissue is associated with shorter overall survival. This is a finding that is likely specific to the role of pDCs in malignancy [68, 76, 77].

TLR4 and HMGB1 are necessary for the generation of an immune response to dying cancer cells. TLR4 expression by DCs was found to be a prerequisite for efficient antigen presentation of tumor antigens furnished by dying cancer cells after treatment with cytotoxic therapy. In order for chemotherapy- or radiotherapy-induced cell death to be translated into an adaptive antitumor immune response, DCs required signaling through TLR4 and its MyD88 adaptor [69]. Injection of HMGB1-neutralizing antibodies inhibited the priming of T cells induced by injured tumor cells. TLR4 mutant DCs (TLR4Asp299Gly), which reduce the binding of HMGB1 to TLR4, did not mature in the presence of dying tumor cells and this was associated with diminished survival in women with breast cancer.

The clinical impact of the TLR4Asp299Gly polymorphism in humans has also been described by Apetoh et al. [69]. In patients treated with anthracyclines, the frequency of breast cancer metastases at 5 years after surgery was statistically higher in patients carrying the TLR4Asp299Gly versus the normal genotype (40 vs. 26.5%; $p < 0.05$). This polymorphism is found in 8–10% of Caucasians, and may compromise the efficacy of breast cancer chemotherapy in this subset of patients.

ATP, another DAMP that may be released by injured tumors cells, has recently been found to be important in DC activation. The $P2RX_7$ ligand ATP is released from dying tumor cells and subsequently activates the inflammasome NLRP3, ultimately leading to IL-1β release and the priming of cytotoxic T cells. Similar to TLR4 polymorphisms, $P2RX_7$ mutations have clinical relevance. In breast cancer patients treated with anthracyclines, the $P2RX_7$ loss-of-function allele had a significant negative prognostic impact on metastatic disease-free survival [78].

While DCs are critically important in developing a tumoricidal immune response, there is also evidence that DCs in the tumor microenvironment are immature, and not only incapable of activating effective antitumor cytotoxic responses, but also inducing tolerance [79, 80]. Through the aberrant activation of MAPK and STAT3, tumors can secrete multiple factors, including IL-10, TGF-β1, VEGF, VIP and IL-6 among others, that modulate DC function and favor tolerogenic DCs [81–83]. Tolerogenic DCs in addition to tumor-conditioned pDCs contribute to T cell anergy and regulatory T cell development in the tumor microenvironment [84]. Regulatory T cells partake in restraining antitumor immunity and maintaining an immunosuppressive environment within malignancies [85]. Recently, there has been further elucidation on signaling pathways that lead to tolerance within DCs. Two pathways which promote Th2 responses, leading to maturation resistant and ultimately tolerogenic DCs, are β-catenin and IL-33 signaling [86–90]. IL-33

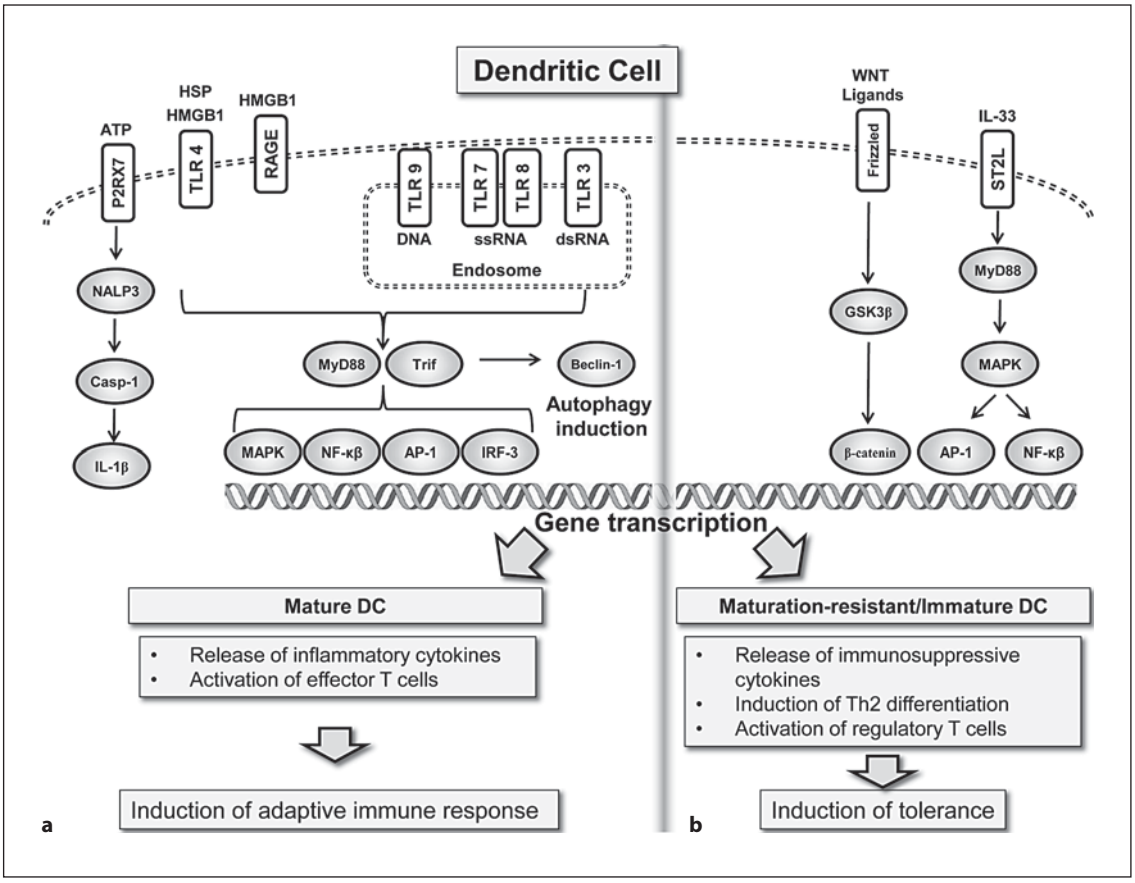


**Fig. 1.** Schematic summary of the role that DAMPs play in the induction of an adaptive immune response. **a** DCs may be induced by DAMPs to mature, leading to the expression of antigen-loaded MHC class I/II molecules, costimulatory molecules and inflammatory cytokines, and gaining the capacity for migration in order to induce effector T cell development. **b** DCs may also be stimulated to enter into a maturation-resistant or tolerance-inducing state, abrogating the development of an adaptive immune response.

is a member of the IL-1 cytokine family that is unique from other family members in that it predominantly leads to a Th2 response [86–88]. However, the role that these and other molecules leading to tolerogenic DCs play in the response to malignancy along with other disease processes remain to be determined.

Therefore, further knowledge of the interaction between DCs and DAMPs in cancer may allow us to exploit their decisive role in inducing immunity, targeting an adaptive immune response against tumor antigens. A clear understanding of the activation of DCs will allow for the development of therapeutic options for cancer patients, such as ex vivo DC vaccine development [91].

### Ischemia Reperfusion Injury

The roles of DAMPs and PRRs in models of sterile inflammation have previously been established [25, 92]. The role of DCs in models of sterile inflammation such as IR injury can help to further elucidate the complex interactions between endogenous 'danger signaling' and DC activation. IR injury is a clinically relevant condition, in which the host response to DAMPs induces exuberant immune activation, resulting in cell death, and possibly organ system failure [93]. The importance of DCs in IR has been most extensively been studied in the kidney and liver [42, 65, 66, 94–96], with less known about the interplay of DCs and IR in the heart and intestine [97, 98].

Consistent with the overall function of DCs in the liver, typically considered to be tolerogenic, the role of DCs

in liver IR injury seems to be primarily protective, with the ablation of hepatic cDCs worsening injury. Liver IR activates DCs, leading to consequent secretion of anti-inflammatory cytokines such as IL-10 and TGF-β [66, 96]. The release is mediated by hepatocyte DNA release leading to the activation of TLR9. However, the precise role of DCs in the liver may be more elusive. Other studies have shown that in hepatic IR, DCs can promote injury by a TLR4-dependent pathway involving HMGB1 [42]. Needless to say, the role of DCs in the liver is complex and requires further study.

In kidney IR, there is a rapid activation of the innate immune system with increased infiltration and activation of DCs that is associated with increased expression of TLR2, TLR4 and the DAMP, HSP70 [94]. Similarly, intestinal IR leads to an increased number of DCs within the tissue. This is associated with increased levels of the nucleotide-binding oligomerization domain, containing 2 (NOD2), TLR4 and HMGB1 [98]. The coordination of the adaptive immune response by DCs in kidney IR injury is likely dependent on a balance of activating signals, such as DAMPs, and inhibitory signaling pathways, such as IRF4 [99].

## Conclusion

In the danger model, immune activation is mediated by ligand binding of PAMPs or DAMPs to archaic germline-encoded PRR [24]. Initially, our knowledge of the receptors and their respective ligands was limited to that of pathogen-derived molecules, e.g. TLR4 and LPS. Over the last 20 years, our knowledge of these critical components of the innate immune system has grown greatly. Now we know that in addition to PAMPs, there are a multitude of endogenously derived molecules that may active the innate immune system and the subsequent inflammatory response.

As our knowledge of DAMP biology increases, undoubtedly other key molecules will be revealed to control DC function. This review summarizes the current knowledge of the role that DAMPs play in DC function (fig. 1). Interestingly, the role of DAMPs in modulating DC function is not always clear-cut, with heterogeneous responses that include not only the expected differences between the different subtypes but also differences based on their origin and location. The capability to harness a DC's capacity to either orchestrate an immune response or induce tolerance is a powerful tool with many clinical applications. For example, the DC may be activated against tumor antigens inducing immunity, or possibly induce allograft tolerance by blockading of PRRs at the time of transplant.

## Disclosure Statement

None of the authors has identified a conflict of interest.

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