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CD24-Siglec G/10 discriminates danger- from pathogen-associated molecular patterns

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Abstract

It is now well accepted that the innate immune system recognizes both damage (or danger)- and pathogen-associated molecular patterns (DAMP and PAMP, respectively) through pattern recognition receptors, such as Toll-like receptors (TLR) and/or Nod-like receptors (NLR). Less clear are whether and how the response to PAMP and DAMP are differentially regulated. The answers may reveal whether the primary goal of the immune system is to defend against infections or to alert the host of tissue injuries. We demonstrated recently that the host response to DAMP is controlled by a DAMP-CD24-Siglec axis. Here we propose a key role for the CD24-Siglec pathway in discriminating between DAMPs and PAMPs.

Introduction

According to popular myth, Ilya Metchnikoff first demonstrated cell-mediated immunity by sticking a rose thorn into starfish larvae. Though this was taught to generations of immunology students as a response to a foreign body, it may in fact be a host response to injury. The fact that the latter possibility was usually over-looked reflects the desire of immunologists to view the immune system as the host's machinery for self-nonself discrimination based on the precise recognition of antigens by clonally distributed receptors on T and B lymphocytes.

Over 20 years ago, in his introduction to the Cold Spring Harbor Quantitative Biology Symposium [1], Charles Janeway elegantly outlined a case against what he called the "Landsteinian Fallacy", namely, all antigenic variations that are recognizable by antibodies must be equally immunogenic. He proposed pattern recognition as the basis for initiation of an immune response against the infectious nonself, in progressively more definitive terms [1–4]. At this time, one of us (YL) was privileged to be working in the Janeway laboratory and showed that components from microbes (including viruses, bacteria, and yeast) can induce costimulatory activity on antigen-presenting cells (APC) [5]. We further showed that induction of the costimulatory molecule B7 (CD80) explained [6] our earlier observation [7] of "immunological help for the cytotoxic T cell response" by activated B cells. These observations validated the Janeway postulate that innate immunity sets the stage for adaptive immunity through its induction of costimulatory molecules on the APC.

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Subsequently, Medzhitov assayed induction of the costimulatory molecule B7 when he cracked the code of microbial pattern recognition by Toll-like receptors (TLR) with Janeway [8]. This study marked a paradigm shift in the concept of immune recognition. A recent account of the exciting time and the periods that followed was recently provided by Medzhitov [9] in commemoration of the 20 year's anniversary of the publication of Janeway's classic assay. Readers are therefore referred to this review.

As a distinct repudiation of clonal receptor-based immune recognition, Matzinger proposed what is known as the "danger theory" in 1994 [10]. In essence, she argued that the immune system does not care about discriminating self- from nonself, but rather dangerous from non-dangerous signals. She acknowledged the difficulty in defining "danger" but equated it to tissue injury occurring in some context. While both Janeway and Matzinger attempted to invoke a nonclonal event as the on-off switch of immunity, they predicted very different purposes of the immune response: to combat infection or to alert the host to tissue injuries. Although tissue injury will certainly occur during infection, those in the Janeway school of thoughts had difficulties reconciling with the danger theory for two reasons. First, from an evolutionary perspective, it is likely that infections impose selective pressure to shape the immune system. Second, the "danger" of the danger theory is that it would predict that the host mounts an immune response whenever tissue injury occurs. Nevertheless, Nature surprised us all when the molecular mechanisms of the host response to pathogen- and danger-associated molecular patterns were revealed over subsequent years.

Shared mechanisms in the recognition of DAMPs and PAMPs

Tissue injuries often lead to release of intracellular components that are collectively called DAMP. Only a few selective examples are provided herein to illustrate the shared mechanisms for recognition of DAMPs and PAMPs. Readers are referred to recent reviews among many outstanding ones for more thorough analyses of DAMPs [11,12].

The best characterized DAMPs in the cytoplasm are the heat-shock proteins (HSPs). It has long been recognized that HSPs can promote immune responses. In addition to their role in promoting antigen-presentation [13,14], some HSP also promote dendritic cell (DC) maturation and induce inflammatory cytokines which in turn recruit lymphocytes and myeloid cells into lymph nodes [15,16] Interestingly, these two functions of the HSPs appear to be fulfilled via distinct mechanisms. The cross-presentation of antigens is mainly achieved by interaction between the HSP and CD91 [17,18]. On the other hand, accumulating evidence supports an important role for the TLR-MyD88-NFkB pathway, which was the classic pathway for PAMP recognition, in the recognition of HSPs in the context of DAMP recognition [19–21].

In addition to the cytoplasm components, nuclear components from damaged cells have also been demonstrated to activate the innate immune system. High mobility group box 1 (HMGB1) is a nuclear protein that was initially studied for its role in gene transcription [22–24]. Interestingly, HMGB1 is actively secreted from monocytes, macrophages, and DC following its acetylation [25, 26,27]. It is also rapidly released by all cell types during necrosis [28]. Extracellular HMGB1 interacts with a number of cellular receptors, such as RAGE [29,30], TLR4 [31], TLR2 [32], and TLR9 [33] when HMGB1 is complexed with DNA, Importantly, HMGB1 activates NF-kB via a TLR-MyD88-dependent mechanism [34–36], which is also very similar to pattern recognition associated with infection.

The third category of DAMPs is low molecular weight adjuvants highly concentrated in the cytosol. A systemic approach by Shi *et al*. demonstrated uric acid as the major source of low molecular weight adjuvant from necrotic cells for cross-priming CD8 T cells [37]. Monosodium urate forms crystal and was demonstrated to cause lysosomal damage and activation of Nalp3 [38], which belongs to the family of NOD-like (NLR) receptors [39]. Like TLR, prototypic NLRs,

NOD1 and NOD2 regulate host response to microbial components [40]. Therefore, although much of the signaling pathways remain to be identified, the major categories of DAMPs studied so far appear to use the same receptors that were characterized for PAMPs.

The unexpected convergence of molecular pathways responsible for recognition of PAMPs and DAMPs raised the question of whether the host really treats PAMPs and DAMPs in fundamentally the same way in terms of the intensity and quality of innate and adaptive immune responses. Unlike those with persistent or chronic infections, those hosts that survive acute infections are often followed by sterilizing immunity. On the other hand, tissue injuries alone are not normally followed by devastating autoimmune diseases. For example in the context of cancer immunity, the interaction between HMGB1 and TLR4 is essential for DC activation, priming of antigen-specific T cells, and resistance to cancer cells [36]. However, despite the fact that tumor lysates are expected to contain a large load of self-antigens, autoimmune side effects were not reported [36]. In the case of HSPs, it has been reported that a co-injection of HSP70, which is also released in conjunction with necrosis, induced diabetes in mice that expressed a T cell receptor (TCR) specific for a viral antigen transgenically expressed in pancreatic islet β-cells[19]. It should be noted, however, that in mice with a normal T-cell repertoire, no autoimmune disease has been reported to be elicited by the same treatment regimen[19]. Likewise, although ectopic expression of membrane-bound GP96 (another HSP)has been demonstrated to trigger signs of autoimmune diseases, the autoimmune phenotype is relatively modest [41].

The fortunate modesty of autoimmune diseases triggered by DAMP is not fully understood but at least two explanations can be invoked. The first involves the well documented mechanism of immune tolerance, such as negative selection of T, B cell receptor repertoire, clonal anergy, activation-induced cell death of mature T cells and the action of suppressor or regulatory cells. Although relatively under-studied, a second intriguing possibility is that the host may have developed a mechanism to ameliorate the response to DAMPs. Our recent studies on the CD24-Siglec G/10 pathway described below are consistent with this notion.

The CD24-Siglec G/10 pathway discriminates between DAMP vs. PAMP

CD24 is also known as the heat-stable antigen (HSA) [42]. It is expressed as a glycosyl-phosphatidyl-inositol (GPI)-anchored molecule [43] and has a wide distribution in diverse cell lineages [44]. Because of the tendency of CD24 to be expressed on immature cells, it has also been used along with other molecules as a stem cell marker during lymphocyte differentiation. The first function associated with CD24 is a costimulatory activity for antigen-specific T cell responses [45–47]. *In vivo* studies indicated that, as a costimulator for T cell activation in lymphoid organs, CD24 is redundant but becomes essential in the absence of CD28 [48,49]. This would not be the case for local target organs that are not as “costimulatory ligand rich” such as the central nervous system. Consistent with this notion, we demonstrated that mice with a targeted mutation of CD24 are completely resistant to induction of experimental autoimmune encephalomyelitis (EAE) [50, 51]. Polymorphisms of human CD24 are associated with risk and progression of several autoimmune diseases [52–56].

While all the above findings can be interpreted in the context of an immune enhancing effect of the CD24 gene, two lines of recent observations pointed to another important role for CD24 in negative regulation of the immune response. First, when wild-type T cells were transferred into lymphopenic, CD24-deficient hosts, they underwent vigorous homeostatic proliferation [57]. In fact, the transferred syngeneic wild-type T cells killed the majority of the CD24-deficient recipients within 2 weeks, possibly due to a “cytokine storm” associated with excessive T cell activation. Further analysis of this model system implicated a role for CD24 on recipient DC in the suppression of excessive homeostatic proliferation [57]. Second, using an acetaminophen-

induced liver injury model, we demonstrated that germline mutation of CD24 dramatically increased susceptibility to necrosis of liver cells [58].

To dissect the molecular basis of this negative regulatory function, we identified molecules that co-immunoprecipitated with CD24 using mass spectrometry. An association between CD24 and HMGB1 was confirmed by reciprocal immunoprecipitation. Likewise, both approaches also revealed interaction between CD24 and Hsp70 or Hsp90. Furthermore, using high affinity neutralizing anti-HMGB1 antibodies [59], we were able to demonstrate a critical role for HMGB1 in the lethal inflammatory response in the CD24-deficient mice.

Theoretically, CD24 may repress host the response to DAMPs by two mechanisms. First, CD24 may trap DAMPs and thus prevent them from binding to their agonistic receptors such as TLR or NLR. In addition, CD24 might actively repress the host response to DAMPs. Since CD24 is a GPI-anchored molecule that does not have an intracellular domain, we reasoned that CD24 negatively regulates responses to HMGB1 by interacting with other proteins that recognize saccharides on CD24. We were particularly intrigued by members of the Siglec families that have Ig-like type I transmembrane proteins with an IgV-like domain binding to a sialic acid-containing structure [60,61]. Currently, there are at least 13 Siglecs in humans and 8 in mice. Except for Sn and Siglec H, all other known Siglecs have immunoreceptor tyrosine-based inhibitory motifs (ITIM) or ITIM-like regions in their intracellular domains. As such, it is expected that they have the capacity to recruit the phosphatases SHP-1, SHP2, and possibly SHIP.

Our analysis of a panel of Siglec fusion proteins indicated that CD24 binds to Siglec G in mice and its human homologue Siglec 10 [58]. The interaction between mouse Siglec G and CD24 is confirmed by immunoprecipitation. Mice with a targeted deletion of the entire Siglec G coding region[62] phenocopy CD24-deficient mice in their susceptibility to acetaminophen-induced liver injury [58]. Further, we demonstrated that Siglec G physically associates with CD24, through which it also associates with DAMPs, such as HMGB1, HSP 70, and HSP90 and repressed the response to these DAMPs. The effect is reflected at the level of NF-kB activation [58]. Importantly, at both cellular or organism levels, neither CD24 nor Siglec G regulate the inflammatory response to lipopolysaccharide (LPS) or Poly I:C (TLR4 and TLR3 agonists respectively), the two PAMPs tested so far. Based on these observations, we propose a simple model by which the CD24-Siglec G/10 discriminate DAMP vs. PAMP by selectively repressing the host response to DAMPs (Figure 1).

In essence, we propose CD24 as the main negatively-signaling DAMP receptor whose function is to antagonize the stimulatory DAMP receptors. In its simplest form, we propose that DAMPs cross-link TLR and/or NLR with the CD24-Siglec G/10 complex and thereby brings Siglec-associated SHP-1 to the signaling complex involved in NF-kB activation. This can be achieved by distinct binding sites on DAMPs to either CD24 or TLR/NLR. Alternatively, DAMPs may be multimerized to allow simultaneous binding to multiple receptors even if the binding sites overlap.

Several pieces of evidence support this model. First, CD24 might be uniquely suitable for interacting with a large array of DAMPs because of its extensive glycosylations. In addition to HMGB1 and HSP, CD24 is associated with other intracellular components such as nucleolin [58]. Second, CD24 is the high affinity ligand for Siglec G/10 [58]. In contrast, CD24 may have additional receptors as targeted mutation of Siglec G/10 only partially reduces the binding of CD24-Fc fusion protein to spleen cells [58]. It is therefore possible that additional signaling pathways, including but not limited to members of the Siglec family, may be recruited to discriminate large arrays of DAMPs from PAMPs. Thirdly, we have demonstrated that for the two best studied DAMPs and two well characterized PAMPs, the CD24-Siglec G/10 pathway

selectively represses the response to DAMP but not PAMP, even though HSP, HMGB1 and LPS all interact with TLR4. However, it should be noted that the role of the CD24-Siglec G/10 pathway is demonstrated mostly by genetic studies, so biochemical analyses are urgently needed to provide mechanistic insights. Likewise, the DAMPs and PAMPs tested are fairly limited in scope, so further studies are needed to demonstrate the general applicability of this model.

Coda

Conceptually, identification of a pathway that selectively represses host responses to DAMPs but not PAMPs suggests that the two inflammatory stimuli are treated very differently by the immune system. As such, it is no longer tenable to consider PAMPs as part of a danger signal unleashed during tissueinjury. Practically, identification of the negative regulator pathway might provide us with novel approaches to amplify the local inflammatory response in order to achieve optimal adaptive immunity for cancer therapy. It is of interest that CD24 is essential for the development of EAE and genetic studies with human CD24 polymorphisms suggest its involvement in multiple autoimmune diseases [63]. If the role for CD24 in autoimmune diseases can be generalized, then the targeting of CD24 might expand the local immune response while conveying resistance to autoimmune diseases, which is a major issue in cancer immunotherapy [64]. Conversely, enhancing CD24-signaling might provide added protection from inflammation and/or autoimmune disease following acute tissue injury or trauma. Finally, it has not escaped our attention that many viruses and most pathogenic bacteria express sialidase as their virulence factors [65,66]. By cleaving off sialic acid from CD24, pathogen-expressed sialidase might abrogate the negative regulation of DAMPs. This could provide a novel explanation for the massive inflammation associated with these pathogens.

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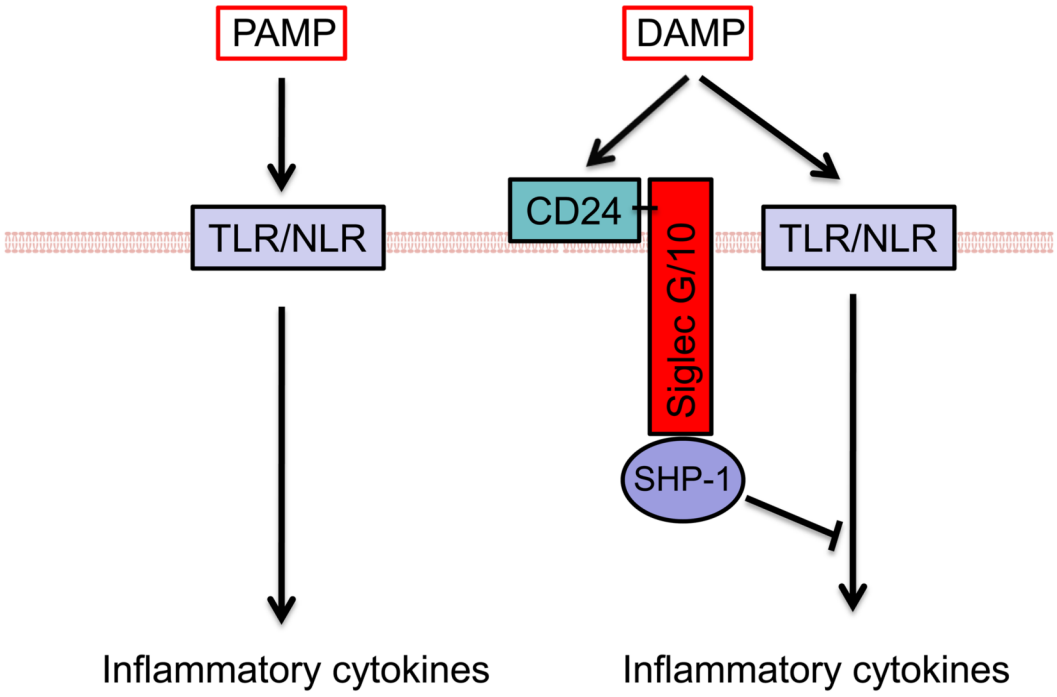

Figure 1.

The CD24-Siglec G (mouse) or -Siglec 10 (human) pathway discriminates between Pathogen-Associated Molecular Patterns (PAMPs) from Danger-Associated Molecular Patterns (DAMPs) by selective repression of the host response to DAMPs. We propose that DAMPs (but not PAMPs) bring CD24-Siglec G/10 into the proximity of TLR/NLR, thus allowing Siglec G/10-associated phosphatases such as SHP1 to repress the DAMP-initiated TLR/NLR signaling. Dysfunction of this pathway might contribute to the etiology of autoimmune disease.