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Sialoside-based Pattern Recognitions Discriminating Infections from Tissue Injuries

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Summary

Recognition of pathogens-associated molecular patterns (PAMPs) by Toll-like receptors (TLR), NOD-like receptors (NLR) and RIG-I-like receptors (RLR) plays a critical role in protecting host against pathogens. In addition, TLR and NLR also recognize danger-associated molecular patterns (DAMPs) to initiate limited innate immune responses. While innate immune response to DAMPs may be important for tissue repairs and wound healing, it is normally well controlled to avoid autoimmune destruction. Recent data support a role for sialoside-based pattern recognition by members of the Siglec family to attenuate innate immunity. In particular, since CD24-Siglec 10/G interaction selectively dampens host response to DAMPs but not PAMPs, this sialoside-based pattern recognition may serve as a foundation to discriminate PAMPs from DAMPs.

Introduction

Over 20 years ago, Charles Janeway proposed the revolutionary concept that the immune system discriminates “infectious nonself from non-infectious self” through pattern recognition [1,2]. With the identification of TLR, NLR, and RLR, pattern recognition is now a major pillar in immunology [3]. However, accumulating data also support Matzinger’s hypothesis [4] that components released during tissue injury, now collectively called DAMPs, also trigger innate immune response, in many cases through TLR [5,6] and NLR [7]. Unlike the sterilizing immunity that follows most infections, innate responses to tissue injuries may actually promote wound healing and tissue repairs [8–10]. Without additional assumptions, it has become difficult to explain how the activation of the same receptors may result in fundamentally different immune responses.

Finding additional pathways of pattern recognition that regulate innate immune response to DAMPs may help to reconcile this paradox. In this review, we will provide an update on major recent advances on innate response to tissue injury and emphasize the role of sialoside-based pattern recognition in negative regulate of innate immune response. Data emerged from this new field may provide a foundation for a new model of innate discrimination of DAMPs and PAMPs.

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New insights from new DAMPs

It has long been demonstrated that tissue injury is associated with inflammation. In the last decade, it has become clear that diverse components from injured tissues or cells are responsible for the inflammatory responses (see [11,12] for recent reviews). Collectively, recent data demonstrate that when released or accumulated during tissue injuries, components from nuclear, cytoplasm, organelle and extracellular matrix may trigger inflammation [11–13]. As updated in Table 1, two categories of DAMPs were added in last two years. The new sources of DAMPs have not only shed light on a potential evolutional link between DAMPs and PAMPs, but have also provided new insights on the pathogenesis of major diseases.

First, recent studies raised the intriguing possibility that mitochondrial DNAs and retroelement DNA may trigger inflammatory response unless they are properly cleared. Mitochondria are believed to be of bacterial origin and retain two pathogen-associated molecular patterns, N-formyl peptides and unmethylated CpG islands. Zhang et al. [14] reported high levels of mitochondrial DNA in blood stream of trauma patients. The pathologically relevant levels of mitochondrial DNA were capable of eliciting secretion of matrix metalloproteinases from, and inducing migration of, polymorphonuclear neutrophils. In combination with synthetic N-formyl peptide, the mitochondrial DNA induces release of the IL-8 by a TLR9-dependent mechanism. Meanwhile, a major breakthrough was reported on immunological basis of Acardi-Goutieres Syndrome (AGS) which exhibits features of both autoimmune diseases and congenital infections. Mutations of five genes (*AGS1-5*) have been identified as genetic causes [15]. Surprisingly, these genes are likely involved in nucleic acid metabolism. Stetson et al. demonstrated that targeted mutation of *Trex1* (*AGS1*) results in accumulation of cytosolic DNA and causes massive activation of type I interferon and lethal autoimmunity that can be cured by mutation of IRF3 [16]. Because of a striking enrichment of endogenous retroelements, it is intriguing that the retroelements may constitute another type of endogenous DAMPs. Since the mitochondria DNA and retroelements are ultimately of microbial origin, it is challenging to develop a conceptual framework relying on simple pattern recognition system to discriminate infections from aseptic tissue damages.

Second, disruption of membrane integrity by crystals likely constitutes another source of DAMPs. Several laboratories demonstrated that crystals formed by uric acids, alum, silica, and cholesterol activated NLRP3 inflammasome [7,17–19]. Instead of directly interacting with DAMPs receptors, the crystals change the intracellular environment, such as ROS and possibly intracellular concentration of potassium [7] [20]. The discovery of a critical role for thioredoxin-interacting protein TXNIP in innate response to crystals links oxidative stress to inflammasome activation[20].

The inflammatory potential of diverse crystals has provided new insights to pathogenesis of several major diseases. For instance, the NLRP3-dependent production of IL1β provides a plausible explanation for the lung fibrosis associated with inhalation of asbestos and silica, called asbestosis and silicosis, respectively [7]. Inflammation associated with gout is now attributed to NLRP3-dependent induction of IL1β by monosodium urate crystals [7] [17]. More data suggest that cholesterol crystals may trigger atherosclerosis [19]. Alum crystals, the classic adjuvant used for vaccination, activate IL1β production by similar mechanisms [21–23][24,25]. Data reported by three independent groups [21–23] showed a critical role for NLRP3 in adjuvant activity of alum. Two other studies [24,25], however, reported that inactivation of NLRP3 did not have a measurable effect on the adjuvant activity of alum. Additional studies are needed to clarify the inconsistencies.

Sialoside-based pattern recognition as a negative regulator for innate immune responses

Innate immune response initiated by TLR and NLR also consists of negative feedback mechanisms to limit the potential damage to the host. Readers are referred to two recent reviews on the identities and functions of negative feedback mechanisms [13,26]. However, it is less clear whether a dedicated recognition pathway may serve as negative regulator for innate immune responses.

A long-standing puzzle in leukocyte biology is how desialyation increase their functions, as demonstrated by increased T cell activation [27], NK cytotoxicity [28] and macrophage phagocytosis [29]. Over 20 years ago, Crocker and Gordon [30] identified what has since emerged as the founding member of the family of sialic acid-binding immunoglobulin-like lectins, now called Siglec [31]. At least 13 members in human and 9 members in the mice have been identified [32]. All but one member have been shown to bind sialioside-containing structures with different specificities. In addition, all but 2 members have intracellular domains with ITIM or ITIM-like domains. The Siglec ITIM domains have been shown to be associated with SHP-1 and SHP-2 phophatase [32]. Cross-linking by either antibodies or synthetic oligosaccharides has been shown to inhibit both innate and adaptive immune responses [32].

An important immune function of Siglec is recently demonstrated by a massive increase of B1 B cells and natural IgM antibodies in mice with targeted mutation of Siglec G [33,34]. However, for the most part, the biological functions and natural ligands of the Siglecs remained elusive. This gap is now being filled by a recent study by Chen et al. who demonstrated interaction between CD24 and Siglec G in mice and Siglec 10 in human [35]. Since the binding of Siglec 10/G to spleen cells is abrogated by targeted mutation of CD24, CD24 is the major ligand for Siglec 10/G on the spleen cells.

Mature CD24 consists of 27–30 amino acids and is anchored to the plasma membrane through a glycosylphosphatidylinositol tail. However, with approximately 50% of the amino acids as potential glycosylation sites, more than 80% of molecular mass are derived from glycosylation [36,37]. The diverse and heterogenous glycosylation may allow CD24 to present a diverse array of DAMPs. Indeed, massspectrometry of CD24-associated protein identifies several prominent DAMPs, including HSP70, 90, HMGB1, Nucleolin and others [35]. Two lines of genetic evidence demonstrate that CD24-Siglec G interaction is an important negative regulator in host response to DAMPs [35]. First, targeted mutation of either CD24 or Siglec G greatly increased NFκb activation and production of inflammatory cytokines by bone marrow-derived dendritic cells to a variety of DAMPs, including HMGB1, HSP70 and HSP90. Second, mice with targeted mutations of either *CD24* or *Siglecg* genes exhibit much higher susceptibility to acetaminophen-induced liver injury. Since the increased susceptibility is abrogated by anti-HMGB1 mAb, CD24-Siglec G interaction is a negative regulator for host response to DAMPs.

Discriminating DAMPs from PAMPs by sialoside-based pattern recognition

It has been largely overlooked that identification of endogenous ligands for TLR and NLR makes it difficult for one to use these receptor to discriminate “infectious nonself from noninfectious self”, as originally envisioned by Charles Janeway. One way to reconcile the Janeway concept with host response to DAMPs is to propose a selective regulatory pathway to discriminate DAMPs from PAMPs. Chen et al. [35] reported that CD24-Siglec G interaction repressed inflammatory responses to HMGB1 and HSP70, 90, but not LPS and PolyI:C, the prototypic PAMPs that stimulate TLR4 and TLR3, respectively. If this

selectivity can be extended to other DAMPs and PAMPs, the sialoside-based pattern recognition may be used to discriminate DAMPs from PAMPs.

An important feature of sialoside-based pattern recognition is its susceptibility to sialidase. Since sialidasesare is commonly expressed by pathogens [38], the host may mount a stronger inflammatory response during infection as the sialoside-based negative regulatory mechanism may be disarmed by pathogen sialidase. In addition, at least 4 sialidases, Neu1-4, are expressed in mammalian cells. Neu3, the only known cell-surface sialidase, is over-expressed in a number of cancer tissues [39–43]. Over-expression of sialidase in cancer cells may provide a mechanism to exacerbate inflammatory response under pathological conditions, thus providing a second mechanism to discriminate “infectious nonself from noninfectious self”.

Since mimicry is a sincere form of flattery, one may get a glimpse of the significance of sialoside-based negative regulation through the molecular mimicry by survivors of the immune system, i.e. pathogens and cancer cells. While machinery of sialyation is believed to be evolved in higher organisms, a number of pathogenic bacteria are known to have acquired either the enzymes to synthesize the sialosides or pre-synthesized sialosides from the host [32]. Carlin et al. [49] demonstrated that interaction between sialyated capsular polysaccharide of group B *Streptococcus* and Siglec 9 dampened the neutrophil defense. Moreover, cancers are known to over-express sialyated glycan either on cell surface (STn, MUC1) or as secreted forms (Soluble mucin 16, CA125). Since these markers have been used for cancer diagnosis, it is of interest to consider whether they may represent a mechanism of immune evasion by cancer. Belisle et al demonstrated [50] that mucin secreted by cancer cells also binds to Siglec 9, a putative negative regulator for activation of neutrophil [49], monocytes and NK cells [51].

Concluding remarks

Taken together, the new model, as illustrated in Fig. 1, envisions two mechanisms to explain how a stronger inflammatory response may be induced following infection. On the one hand, the sialoside-based pattern recognition down-regulates host responses to DAMPs without affecting those to PAMPs. On the other hand, pathogen sialdases may exacerbate inflammation during infection by disrupting CD24-Siglec G/10 interaction. Both mechanisms, working together, enable the pattern recognition receptors to distinguish “infectious nonself from noninfectious self”. The recent discoveries of genetic control of autoimmune diseases either by CD24 [44–47] or by sialic acid acetylesterase [48] suggest dysregulation of this pathway as a cause for autoimmune diseases.

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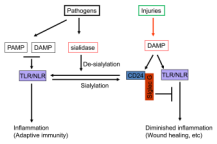

Fig. 1.

Sialoside-based pattern recognition discriminates infections from aseptic tissue injuries by two possible mechanisms. First, CD24 forms trimolecular complex with DAMPs and Siglec G that inhibits activation of TLR/NLR. Second, pathogen-encoded sialidases prevent CD24 from interacting with Siglec G. As a result, DAMPs and PAMPs become indistinguishable during infection.

Table 1

Two new categories of DAMPs

DAMPs	Receptors/Sensors
I. Evolutionary culprit	
Retroelements	ND
Mitochondria DNA	TLR9
Formyl peptides	FPRL1/2
II. Disruption of membrane integrity	
Monosodium urate crystal	NLRP3
Uric acid	NLRP3
Cholesterol crystals	NLRP3
Alum	NLRP3