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LETTER TO THE GLYCO-FORUM

Since there are PAMPs and DAMPs, there must be SAMPs? Glycan "self-associated molecular patterns" dampen innate immunity, but pathogens can mimic them

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The ~500-million-year-old adaptive immune system detects foreign ("non-self") epitopes via B cell-derived antibodies and/or T cell receptor interactions with major histocompatibility complex (MHC)/peptide complexes (Hedrick 2004). Cells of the more ancient innate immune system display receptors that detect foreign glycans, for example, fungal glycan recognition by the macrophage mannose receptor (Stahl and Ezekowitz 1998) or by circulating collectins and pentraxins (Bottazzi et al. 2010). The latter field was revolutionized by definition of "pathogen-associated molecular patterns" (PAMPs; Medzhitov and Janeway 1997), microbial products that can be detected by pattern recognition receptors (PRRs), particularly the Toll-like receptors (TLRs; Beutler 2009), Nod-like receptors (Davis et al. 2011) and dendritic cell receptors such as C-type lectins (Geijtenbeek et al. 2004). Many PAMPs are glycoconjugates (e.g., bacterial lipo-oligosaccharides) or glycan-based polymers (e.g., bacterial peptidoglycans), including bacterial DNA or viral RNA (which are (deoxy)ribose-based polymers). The innate immune system also recognizes "danger-associated molecular patterns" (DAMPs; Matzinger 2002; Chen and Nunez 2010), molecules released during tissue damage, such as heat-shock proteins, high mobility group box 1 (Lotze and Tracey 2005), hyaluronan (HA) fragments (Taylor and Gallo 2006), glycosaminoglycan (GAG)-bearing matrix proteoglycans (Moreth et al. 2010) and certain crystals (Martinon et al. 2009), all of which originate from damaged host cells or matrices. Signals initiated by DAMPs and PAMPs are transduced via similar pathways, activating innate immune inflammatory responses.

Since the innate immune system recognizes invaders via PAMPs and endogenous damage via DAMPs, it is reasonable to suggest a class of "self-associated molecular patterns" (SAMPs), which would be recognized by intrinsic inhibitory receptors, to maintain the baseline non-activated state of innate immune cells and dampen their reactivity following an immune response. In this regard, note that circulating cells of the innate immune system (neutrophils, monocytes etc.) remain quiescent in the bloodstream under normal conditions, and only become activated as they routinely enter into extravascular spaces and encounter PAMPs or DAMPs, and/or are subjected to experimental manipulations in vitro.

The term "SAMP" was suggested once before, but referred not to patterns, but to proteins such as complement regulatory protein CD200 (Elward and Gasque 2003). Such defined molecules mediating protein:protein interactions are not really "patterns", but more akin to how MHC molecules are recognized as "self" by natural killer cells (Parham 2008). What might be the true SAMPs for inhibitory feedback on innate immunity? Given their dominance on cell surfaces and extracellular matrices, the likely candidates are "self" glycans, of the kind not easily confused with PAMPs and DAMPs. Glycans that best fit this criterion are sialic acids, which are found primarily on cells of the deuterostome lineage of animals (Varki and Schauer 2009). Other candidates are GAGs such as sulfated heparan and dermatan sulfate (Esko et al. 2009); glycans that evolved only in multicellular animal forms (Varki et al. 2009).

To detect such SAMPs, there must be cognate Self-PRRs (SPPRs). The first-studied example was factor H, a serum protein which restricts alternate complement pathway activation on host cell surfaces by recognizing "self" in the form of sialic acid-containing patterns on cell surfaces. Factor H also recognizes heparan/heparin sulfate GAGs as "self", apparently via the same anion binding domains that recognize sialic acids (Pangburn et al. 2000; Kajander et al. 2011). Indeed, naturally occurring mutations of these anion-binding domains of factor H are associated with unwanted innate immune reactivity (Herbert et al. 2007). Interestingly, efforts to identify structurally defined glycan ligands of factor H have failed. Rather, recognition involves certain polyanionic "self" patterns on cell surfaces. And factor H is evolving to best recognize such patterns (Granoff et al. 2009).

The second class of SPPRs are the Siglecs (sialic acid recognizing Ig-like lectins), which have N-terminal V-set Ig-like

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domains that recognize sialic acids and often have tyrosine-based inhibitory signaling motifs within their cytosolic tails (Varki and Crocker 2009; Cao and Crocker 2011). Ongoing work on the CD33-related subset of inhibitory Siglecs indicates that they recognize sialic acid patterns as "self" and deliver inhibitory signals to innate immune cells. Consistent with this notion, deletion of Siglec-F from mouse eosinophils gives a hyperactive response (Zhang et al. 2007); mouse Siglec-G deletion results in over-reactive response to DAMPs and PAMPs (Chen et al. 2009, 2011) and Siglec-8 polymorphisms are associated with asthma risk (Gao et al. 2010). Again, rather than being highly specific sialoglycans, the candidate SAMPs appear to be certain types of sulfated and fucosylated glycans for Siglec-F and Siglec-8 (Bochner et al. 2005; Guo et al. 2011), and as yet undefined glycoforms of the heavily glycosylated CD24 molecule for Siglec-10 (Chen et al. 2011). Indeed Siglec-G (the mouse ortholog of human Siglec-10) apparently uses sialic acids on CD24 as a feedback loop to dampen excessive innate immune responses to sterile inflammation (Chen et al. 2009). Notably, while "CD24" is defined by its very short GPI-anchored polypeptide of 27 amino acids, it is actually a very complex family of molecular patterns, with certain sialoglycoforms likely being recognized by Siglec-G. To avoid inaccurate statements, e.g., "CD24 is the ligand for Siglec-G/10" (Chen et al. 2009), such specific cognate glycoform ligands might best designated by a superscript (Varki 2009). In this nomenclature, $CD24^{SGL}$ would be the designation for the subset of CD24 glycoforms recognized by Siglec-G via its presentation of sialic acids. This would distinguish it from other glycoforms of CD24 recognized by non-SPPRs such as P-selectin ($CD24^{PSL}$) or L-1 ($CD24^{L1L}$; Varki 2009).

However, the "self" sialome of vertebrate hosts is itself rapidly evolving to evade sialic-acid binding pathogens (Varki and Schauer 2009). Thus, the binding preferences of SPPRs such as Siglecs must also evolve rapidly to maintain self-recognition. In keeping with this, the sialic acid-binding Ig-like V-set domains of Siglecs are the most rapidly evolving part of these receptors (Varki and Crocker 2009), and the same is true of the anion-binding domains of factor H (Altheide and Varki, unpublished). In this regard, one can predict that despite being orthologs, mouse Siglec-G and human Siglec-10 will recognize different glycoform subsets of CD24 produced by different human and murine cell types.

Another candidate SAMP is the non-sulfated GAG HA, which is expressed at cell surfaces and extracellular matrices of vertebrate cells (Hascall and Esko 2009). HA fragments generated by matrix injury actually stimulate inflammation through TLR recognition (Termeer et al. 2002; Taylor et al. 2004), and this recognition system has important functional outcomes for inflammation in the skin (Yamasaki et al. 2009) and lung (Jiang et al. 2005). This capacity of HA to be recognized by TLRs that also recognize classical PAMPs results in triggering of the alternative signaling pathways that fine tune the host's response to injury. Thus, in contrast to an uncontrolled pro-inflammatory response to LPS, HA, by the engagement of CD44, results in down-regulation of immune reactivity (Teder et al. 2002; Muto et al. 2009; Jiang et al. 2011).

Given that vertebrates have SAMPs and use SPPRs to recognize them and down-regulate innate immune responses, it is not surprising that microbial commensals and pathogens have evolved SAMP molecular mimics (SAMP-MMs) to take the advantage of SAMPs. For example, a wide variety of human pathogens coat themselves with the type of sialic acid (*N*-acetylneuraminic acid, Neu5Ac) commonly found in humans (Vimr et al. 2004), and these sialoglycan molecular mimics dampen innate immune responses by ligating inhibitory Siglecs (Carlin et al. 2009) and/or factor H (Khatua et al. 2010). Remarkably, such molecular mimicry is achieved not by acquisition of vertebrate genes, but via multiple independent episodes of convergent evolution, generating sialoglycans very similar to the vertebrate host, including details of underlying glycan sequences (Vimr et al. 2004; Lewis et al. 2009). In fact, pathogens have used every conceivable approach to coat themselves with sialic acids or similar molecules. Even the polysialic acids found in the vertebrate brain are mimicked by *Escherichia coli* K1 and *Meningococcus* (Vimr et al. 2004), organisms with a tendency to cause central nervous system infections. And some pathogens even use proteins to mimic host glycans (Schneider et al. 2009).

To date no pathogen seems to have completely reinvented sulfated GAGs, which mediate endogenous vertebrate functions via ensembles of possible motifs. Perhaps for these reasons, these molecules have changed less over evolutionary time. There are some partial mimics, such as the non-sulfated backbones of heparan sulfate (heparosan, synthesized by *Pasteurella multocida*) and chondroitin/dermatan sulfate (chondroitin, synthesized by *E. coli* K4; DeAngelis 2002). Apparently the complexities of animal GAG sulfation are beyond the mimicry capabilities of microbes. Likewise, the conversion of the sialic acid Neu5Ac to *N*-glycolylneuraminic acid (Neu5Gc) has apparently not been achieved by any known bacterial or viral pathogen (Lewis et al. 2009).

Given the potentially lethal consequences of even transient neutropenia due to invasion by commensals, it is evident that the innate immune system is constantly battling to hold back even such microorganisms. In this regard, it is interesting that several pathogens displaying SAMP-MMs are also common commensals. Thus, the consequences of SAMP-MM can be dualistic, initially evolving to achieve commensal states, and becoming virulence factors only when conditions allowed. Regardless of the details, this convergent evolution indicates a strong pressure for successful commensals/pathogens to evolve SAMP-MMs. In this regard, group A *Streptococcus* has reinvented HA and displays it as a high molecular weight capsule (DeAngelis 2002). Perhaps it is also an SAMP mimic ligand of an as yet unknown SPPR, other than CD44?

Given the multitudinous PAMPs and DAMPs, it seems likely that there will be more examples of SAMPs and SPPRs. As with the Siglecs and factor H, such SPPRs are also expected to rapidly evolve in different species, in order to maintain self-glycan recognition. One might even predict feedback loops with increased expression of SAMPs helping to shut down a response to DAMPs or PAMPs. In this regard, endogenous Siglec-F SAMPs are up-regulated during an

eosinophilic inflammatory reaction (Zhang et al. 2007). The nature of such SAMPs is unlikely to be a linear glycan sequence, but rather a broader motif or pattern, perhaps in the form of clustered saccharide patches (Cohen et al. 2009).

A prediction arising is that glycan patterns relatively unique to a given taxon and difficult to mimic by pathogens are also more likely to be utilized as SAMPs. However, taxon- or species-specific changes or losses of glycan-based SAMPs do occur. Circumstances may arise where the evolutionary pressures are strong enough for a population to discard an otherwise useful SAMP glycan that has become the binding target of a lethal pathogen. An example might be the loss of the sialic acid Neu5Gc in the human lineage, which may have occurred due to selection by a malarial organism (Varki and Gagneux 2009). However, Neu5Gc-containing sialoglycans may have also been the preferred binding site for at least some of the ancestral hominid Siglecs (Varki 2010). This loss of a preferred SAMP glycan due to pathogen-related selection may have left the human ancestral innate immune system in an imbalanced state involving loss of self-recognition. Human Siglec-binding sites have since undergone selection to recognize the remaining major sialic acid, Neu5Ac. But many bacteria are capable of reinventing Neu5Ac (and not Neu5Gc) by convergent evolution. Thus, humans may have become optimal targets for SAMP-MM by pathogens that express Neu5Ac-containing surface glycans (Varki 2010).

Further complexity arises due to host activatory responses to SAMPs. For example, some Siglecs generate an activating rather than an inhibitory response (Varki and Crocker 2009; Cao and Crocker 2011). Indeed, in some cases, the binding specificities of the activatory/inhibitory Siglec pair are practically identical, because ongoing gene conversion events involve the exons encoding binding domains (Angata et al. 2006). At present, the most logical explanation for having SPPRs that respond by activation is that they represent ongoing evolutionary responses to molecular mimicry by pathogens (Varki and Crocker 2009; Cao and Crocker 2011).

Much further work is needed to more fully define the diversity and specificity of SAMPs and their cognate SPPRs in each species, their roles in regulating the innate immune response and their potential hijacking by SAMP-MMs.

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Conflict of interest

None declared.

Abbreviations

DAMP, danger-associated molecular pattern; GAG, glycosaminoglycan; HA, hyaluronan; MHC, major histocompatibility complex; Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; SAMP, self-associated molecular pattern; Siglecs, sialic acid recognizing Ig-like lectins; SPPR, self-pattern recognition receptor; TLR, Toll-like receptor.

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