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On self-nonself discrimination in pattern recognition

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Wide distribution and broad reactivity are cardinal features of pattern recognition receptors that allow rapid mobilization of large numbers of effectors to deal with pathogens. However, these features come with significant baggage as the receptors have been shown to interact with many intracellular components, collectively called danger-associated molecular pattern (DAMP) because they are released during necrosis. It is puzzling how the host manages to mount sterilizing immunity to most pathogens and avoids doing fatal damage in response to aseptic tissue injuries. This paradox was reconciled when we revealed a novel pathway mediated by CD24 and its receptor, Siglec G in mice or Siglec 10 in humans. This pathway represses host responses to DAMPs but not pathogen-associated molecular patterns (PAMPs), thus allowing hosts to discriminate PAMP from DAMP. Disruption of this pathway leads to a devastating systemic inflammatory response when necrosis occurs in mice. Therefore, the CD24/Siglec 10 pathway enables a cross-reactive pattern recognition pathway to initiate immunity against pathogens without significant immune-mediated self-destruction in case of tissue injuries.

1 Historical perspective

Vertebrates have evolved to protect themselves against infections by two different means. The first is an innate immunity using non-clonally distributed receptors, while the second is an adaptive immunity using clonally distributed receptors. Because of vast diversity of the clonally distributed receptors, including the T cell receptor and immunoglobulin, the adaptive immune system is capable of precise recognition of essentially all biological structures. The only caveat is that the frequency of an average clone is inversely correlated with the diversity of the repertoire. Therefore, clonal expansion is essential for a measurable and therefore biologically relevant adaptive immune response. As such, the primary defense against infection is mediated by innate immunity, which uses non-clonally distributed receptors and is not limited by the low frequency of effector cells.

Until 20 years ago, the two branches of immunity were considered largely separate. In 1989, Janeway [1] wrote a landmark introduction for the Cold Spring Harbor Quantitative Biology Symposium in which he proposed a revolutionary concept that adaptive immunity is initiated by pattern recognition of innate immunity. At that time, one of us (YL) was working in the Janeway's Laboratory, establishing the induction of costimulatory activity by components of bacteria, yeast and viruses [2]. Our subsequent work [3] demonstrated the need of *cis*-presentation of both antigen and costimulators for T cell activation. While these data proved the concept that innate recognition paves the way to adaptive immunity, the major breakthrough was the discovery by a brilliant fellow from the Janeway's Laboratory, Medzhitov, who identified mammalian Toll homologue of the fruit fly and showed that its activation results in induction of costimulatory molecule B7.1 (CD80) and inflamma-

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tory cytokines [4]. This discovery started what Dr. Ronald German [5] called "the innately interesting decade" of immunology.

2 Two different patterns of innate recognition

The main drive behind the Janeway's Pattern Recognition Theory is to establish a conceptual frame to explain how the host could selectively mount immune response to infectious nonself but not noninfectious self [6]. With the identification of the host function of toll-like receptors (TLR) and their ligands [7], as well as the identification of NOR-like receptors and their potential stimuli [8], it is no longer questionable whether the innate recognition drives the immune system towards the more potent adaptive immune response to pathogens. Whether this pathway differentiates infectious nonself from noninfectious self, as Janeway proposed, remains unclear.

The first challenge came from Polly Matzinger in the form of "danger theory" in 1994 [9]. She argued that the immune system recognizes dangerous vs. nondangerous insults, but the nature of dangers, currently regarded as tissue injury, was not well-defined in her original hypothesis. In support of this notion, intracellular components released during tissue injuries, most notably HMGB1 and the heat-shock proteins have been shown to induce significant, albeit limited inflammatory responses [10–13]. Collectively, these components are called danger-associated molecular patterns, or DAMPs. Surprisingly, the response to these components is also under the control of TLR and NLRs [13,14]. Further, the down-stream signaling events for DAMPs and PAMPs converge at NFkB activation. The obvious question is then whether PAMPs and DAMPs are treated the same way by the innate immune system, and if so, whether the Janeway notion of self-nonself discrimination still holds.

3 CD24-SiglecG/10 pathway discriminates PAMPs from DAMPs

Despite the similarity in the broad outline of their signal transduction pathway, PAMPs and DAMPs are quite distinct in their molecular composition. Therefore, it is plausible that additional pathways that differentially regulate the recognition of DAMPs and PAMPs exist. Our recent observation on the role of the CD24-SiglecG/10 pathway in repressing tissue injuries indicated that this may well be the case.

CD24 is broadly expressed in a number of tissues, including hematopoietic cells, epithelial and neuronal cells. As a rule, CD24 is expressed at higher levels in the immature cells. Therefore, CD24 is also used as markers for multiple lineages of stem cells. Functionally, we have demonstrated that CD24 plays a critical role in the development of autoimmune diseases in both mice and humans [15]. More recently, we demonstrated that mice with targeted mutation of CD24 are extremely sensitive to liver injury induced by acetaminophen [16]. In order to understand the potential mechanisms, we used mass spectrometry to identify CD24-associated molecules. Surprisingly, we found that the major component associated with CD24 is HMGB1, which was a prototypic DAMP. The functional significance of HMGB1 in CD24-regulated tissue injuries was confirmed by neutralization with a high affinity anti-HMGB1 antibody [16].

As CD24 lacked a cytoplasmic domain, we searched for CD24 partners that may serve as inhibitors for innate recognition of HMGB1. We were particularly interested in the Siglec family members as they recognize sialic acid-containing structure and are capable of inhibiting signal transduction through their ITIM motif [17]. We identified SiglecG in mice and Siglec10 in humans that bind to CD24 with high avidity [16]. The significance of CD24-SiglecG/10 interaction has been demonstrated by the fact that SiglecG/10 forms complexes with HMGB1 through CD24 and that mice with targeted mutation of *Siglecg* phenocopy mice with that of *Cd24*. The negative regulation is reflected at the level of dendritic cells (DC) as $Cd24^{-/-}$ DC. $Siglecg^{-/-}$ DC exhibits significantly enhanced response to HMGB1. Significantly, the CD24-SiglecG pathway does not inhibit response to TLP ligands such as lipopolysaccharides (LPS) and Polyinosine-polycytidylic acid (poly I:C) [16].

CD24 may be uniquely suitable to present DAMPs for the negative regulation because the heavy glycosylation allows a diverse array of CD24 molecules to interact with what is likely to be a diverse array of DAMPs. In supporting this notion, we demonstrated that CD24 is associated with and negatively regulates the DC response to HSP70 and HSP90. CD24 also strongly binds to nucleolin [16].

Although more ligands need to be tested, it is already clear that because of the CD24-SiglecG/10 pathway, the innate immune system does not treat DAMPs and PAMPs in the same way. Therefore, it is perhaps not appropriate to consider PAMPs as? part of danger signal [9]. Further investigations are needed to confirm the molecular mechanism by which the CD24-SiglecG complex interacts with the TLR signaling complex.

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1 Janeway C A. Approaching the asymptote? Evolution and revolution in immunology. Cold Spring Harb. Symp Quant Biol, 1989, 54: 1–13
2 Liu Y, Janeway C A Jr. Microbial induction of co-stimulatory activity for CD4 T-cell growth. Int Immunol, 1991, 3: 323–332
3 Liu Y, Janeway C A J. Cells that present both specific ligand and the

costimulatory activity are the most efficient inducer of clonal expansion of normal CD4 T cells. Proc Natl Acad Sci USA, 1992, 89: 3845–3849
4 Medzhitov R, Preston-Hurlburt P, Janeway C A Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature, 1997, 388: 394–397
5 Germain R N. An innately interesting decade of research in immunology. Nat Med, 2004, 10: 1307–1320
6 Janeway C A Jr. The immune system evolved to discriminate infectious nonself from noninfectious self. Immunol Today, 1992, 13: 11–16
7 Medzhitov R. Approaching the asymptote: 20 years later. Immunity, 2009, 30: 766–775
8 Inohara N, Ogura Y, Nunez G. Nods: a family of cytosolic proteins that regulate the host response to pathogens. Curr Opin Microbiol, 2002, 5: 76–80
9 Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol, 1994, 12: 991–1045
10 Scaffidi P, Misteli T, Bianchi M E. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature, 2002, 418: 191–195
11 Wang H, Bloom O, Zhang M, *et al*. HMG-1 as a late mediator of endotoxin lethality in mice. Science, 1999, 285: 248–251
12 Basu S, Binder R J, Suto R, *et al*. Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-kappaB pathway. Int Immunol, 2000, 12: 1539–1546
13 Millar D G, Garza K M, Odermatt B, *et al*. Hsp70 promotes antigen-presenting cell function and converts T-cell tolerance to autoimmunity *in vivo*. Nat Med, 2003, 9: 1469–1476
14 Apetoh L, Ghiringhelli F, Tesniere A, *et al*. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med, 2007, 13: 1050–1059
15 Liu Y, Zheng P. CD24: A genetic checkpoint in T cell homeostasis and autoimmune diseases. Trends Immunol, 2007, 28: 315–320
16 Chen G Y, Tang J, Zheng P, *et al*. CD24 and Siglec-10 Selectively Repress Tissue Damage-Induced Immune Responses. Science, 2009, 323: 1722–1725
17 Crocker P R, Paulson J C, Varki A. Siglecs and their roles in the immune system. Nat Rev Immunol, 2007, 7: 255–266