PERSPECTIVE

Innate Immunity Focus

Inhibitory pattern recognition receptors

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Pathogen- and damage-associated molecular patterns are sensed by the immune system's pattern recognition receptors (PRRs) upon contact with a microbe or damaged tissue. In situations such as contact with commensals or during physiological cell death, the immune system should not respond to these patterns. Hence, immune responses need to be context dependent, but it is not clear how context for molecular pattern recognition is provided. We discuss inhibitory receptors as potential counterparts to activating pattern recognition receptors. We propose a group of inhibitory pattern recognition receptors (iPRRs) that recognize endogenous and microbial patterns associated with danger, homeostasis, or both. We propose that recognition of molecular patterns by iPRRs provides context, helps mediate tolerance to microbes, and helps balance responses to danger signals.

Pattern recognition receptors (PRRs) recognize molecular patterns

The immune system needs to recognize and correct deviations from normal physiology, such as harmful contact with a microbe, disruption and damage of healthy tissue, and malignant transformation of cells. To sense the presence of microbes, the immune system employs a set of PRRs (Janeway, 1989). At present, five classes of PRRs have been defined: the TLRs and the C-type lectin receptors, which are both localized to cell or endosomal membranes; the cytoplasmic NOD-like receptors and RIG-I–like receptors; and additional cytoplasmic DNA sensors, such as cyclic GMP-AMP synthase (Gong et al., 2020; Takeuchi and Akira, 2010). PRRs recognize highly conserved components of microbes, termed pathogen-associated molecular patterns (PAMPs; Akira et al., 2006; Medzhitov and Janeway, 2002). In addition, PRRs sense endogenous molecules associated with damaged and dying cells termed danger- or damage-associated molecular patterns (DAMPs). Many factors are currently considered DAMPs, among which are S100 proteins, heat shock proteins (Hsps), high mobility group box 1 protein (HMGB1), and different glycans such as heparan sulfate (Chen and Nuñez, 2010; Matzinger, 1994; Matzinger, 2002).

The self–nonself model of microbe recognition, first introduced by Frank Macfarlane Burnet and later refined by Charles Janeway, explains how the innate immune system recognizes pathogens through molecular patterns (Burnet, 1959; Janeway, 1989). Because pathogens constantly evolve, they cannot be recognized individually, as this would require an infinite

number of receptors. To circumvent this problem, the immune system recognizes components of microbial cells that are highly conserved (but not identical) among microbes and cannot be subject to quick change or removal by the microbe because they are essential for its survival (Bianchi and Manfredi, 2009). These groups of structurally similar molecules are called PAMPs. One of the first PAMPs to be discovered was LPS of Gram-negative bacteria, which is detected by TLR4, providing activating signals that drive adaptive immunity (Medzhitov et al., 1997; Poltorak et al., 1998). Soon after, many additional PAMPs were discovered, such as the lipoteichoic acid (LTA) of Gram-positive bacteria (Schwandner et al., 1999). Later, Polly Matzinger extended the family of "molecular patterns" by presenting the danger theory of immunity, introducing DAMPs. The term DAMP has since been used in the literature to denote both damage- and danger-associated molecular patterns. Unlike PAMPs, DAMPs are not defined structurally, and there is (following Janeway's argument) little need for that: there are only a finite number of host molecules. Instead, DAMPs are defined contextually: they signal danger, and what is dangerous in one place is not necessarily dangerous in another. Such a model is not easily addressed experimentally because of this elusive definition of danger (Pradeu and Cooper, 2012). As highlighted by Pradeu and Cooper (2012), Matzinger later clarified that while the model is theoretical, the idea behind it is that the immune system responds to damage (Matzinger, 2002), and damage signals are much easier to define than danger signals. Since then, many more groups of molecular patterns have been

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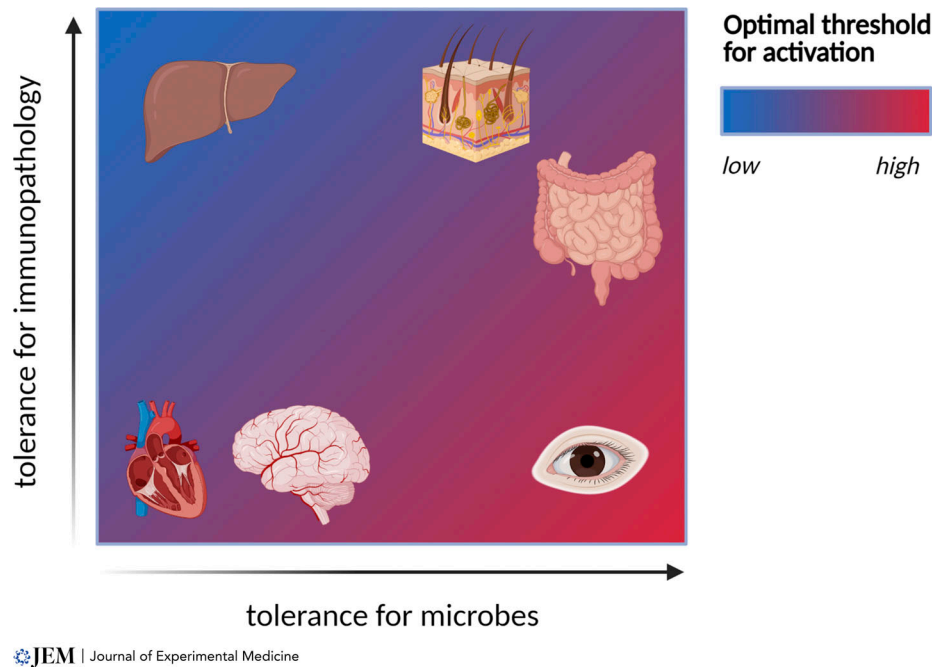Correspondence to Linde Meyaard: l.meyaard@umcutrecht.nl.

Figure 1. **The optimal threshold for activation is context dependent.** The required threshold for activation of immune cells differs per location and depends on (1) the tolerance of the organ for immune pathology and (2) the tolerance to microbial exposure. Organs with a high regenerative capacity, such as the liver, are more able to deal with immunopathology than organs with low regenerative capacity, such as the heart or the brain. The gut and skin are constantly exposed to microbes, most of which are harmless or beneficial and should be tolerated. The eye can tolerate a certain amount of microbial exposure, and the cost of responding to a microbial stimulus will be high, so a high threshold will ensure the response occurs only when needed. In different organs, either tolerance for microbes or tolerance for immunopathology may be more important in determining the optimal threshold for activation.

put forward, among which are resolution-, metabolism-, commensal-, and homeostasis-associated molecular patterns (HAMPs; Cario et al., 2002; Greslehner, 2020; Li et al., 2019; Shields et al., 2011; Wang et al., 2020). Under the term molecular pattern, we now classify groups of molecules that signal the occurrence of a particular event, that elicit similar effects, and that may share common structural features.
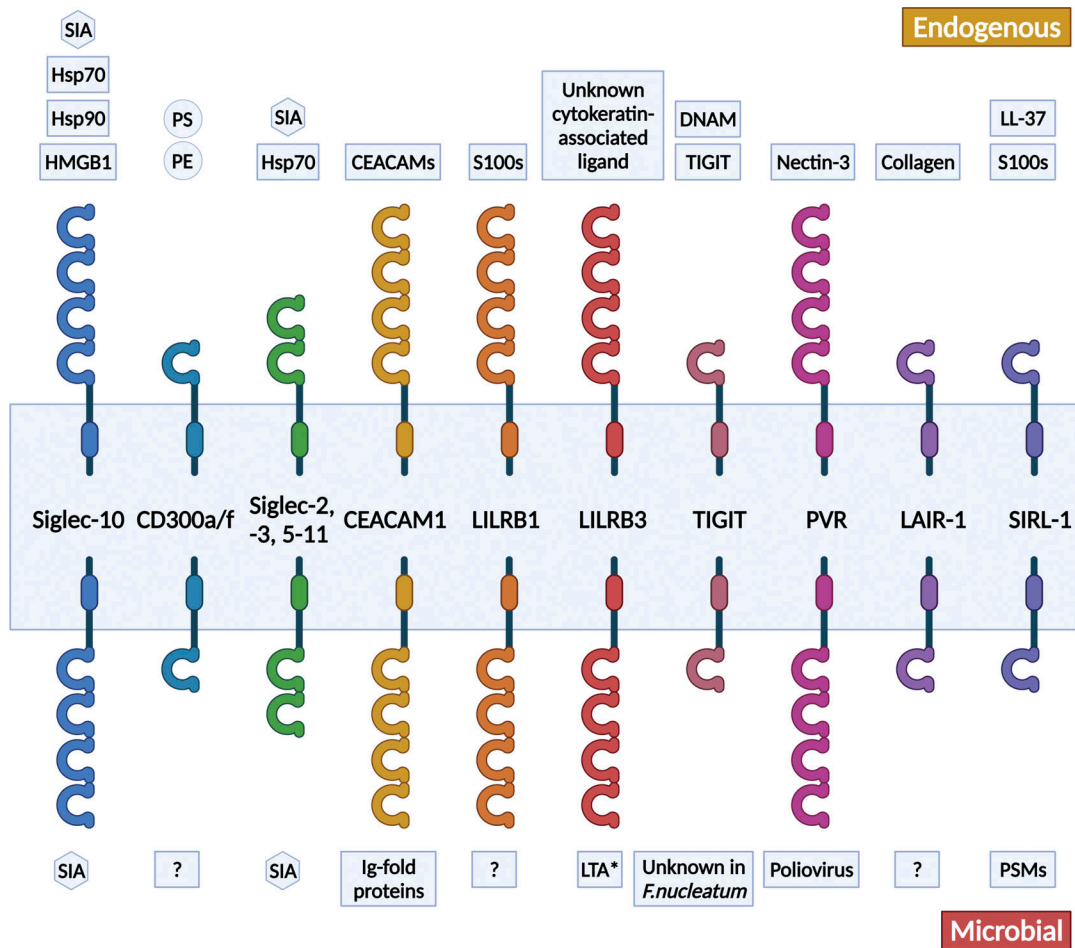
Immune responses are context dependent

The same molecular pattern does not always evoke the same response. Different microbes inevitably colonize barrier tissues such as the skin and gastrointestinal tract, and most of them are not harmful or even provide benefit to the host, yet still express PAMPs. Similarly, while tissue damage and cell death can be pathologic, cell death can also be part of normal physiology and tissue renewal. To distinguish harmless from potentially harmful circumstances, the immune system must correctly interpret the activating signals molecular patterns are delivering, and therefore the threshold for immune system activation needs to vary by context. Tissues that are highly exposed to microbes, such as the gut and skin, require a high activation threshold to tolerate most microbes, whereas in the circulation, a low activation threshold is required to respond to all microbes (Fig. 1). Furthermore, not all tissues can tolerate tissue damage to the same extent. In situations where inflammatory responses result in more damage to the organism than the disturbance itself, not responding to disturbances is the best strategy (Medzhitov et al., 2012). Following this argument, the threshold for immune

activation needs to be higher in organs with low regenerative capacity, such as the heart or brain, where an inflammatory response can lead to detrimental consequences, versus organs with a high regenerative capacity, such as the liver (Fig. 1). Hence, the immune response needs to be context dependent, and it is not clear how context for molecular pattern recognition is provided.

Immune inhibitory receptors dampen immune system activation

Immune inhibitory receptors are germline-encoded innate receptors relaying inhibitory signals to immune cells. Much about their functioning has been learned by studying programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte protein 4 (CTLA-4), and killer cell Ig-like inhibitory receptors on NK cells (Long, 2008; Ravetch and Lanier, 2000; Rowshanravan et al., 2018). Inhibitory receptors attenuate activating signals coming from activating receptors and fine-tune the level of activation of an immune cell. Most of them relay the inhibitory signals via one or more immunoreceptor tyrosine-based inhibitory motifs (ITIMs) present in their cytoplasmic tails. ITIMs have the consensus sequence V/L/I/SxYxxV/L/I (Vivier and Daëron, 1997). When immune inhibitory receptors are activated by their ligands, the ITIMs recruit tyrosine phosphatases, which dephosphorylate the cytoplasmic tails of activating receptors or key molecules in their signaling pathways (Coxon et al., 2017; Gergely et al., 1999). The ligands for many inhibitory receptors are still unknown, while some single-molecule ligands have

Figure 2. **iPRRs and their endogenous and microbial ligands.** The currently known group of iPRRs consist of CD300a/f, Siglecs 2, 3, and 5–11, CEACAM1, LILRB1 and LILRB3, TIGIT, poliovirus receptor (PVR), LAIR-1, and SIRL-1. The upper part of the figure displays endogenous ligands, and the bottom part displays the microbial ligands for iPRRs. For most receptors, both endogenous and exogenous ligands have been identified. Protein ligands are depicted as rectangles, lipids as circles, and carbohydrates as hexagons. All inhibitory receptors depicted are composed of Ig domains, and the number of Ig domains is schematically depicted for each receptor. In humans, most of these receptors are located in the chromosomal region 19q13, except CD300a/f (17q25) and TIGIT (3q13). *, LTA is a ligand for the mouse orthologue of the human LILRB3. PSM, phenol-soluble modulin; S100s, S100 proteins; SIA, sialic acid.

been identified for others. We previously argued that immune inhibitory receptors regulate immune responses in different ways. They may set a threshold for immune cell activation by preventing activating receptor signaling in certain contexts or dampen activating receptor signaling after it has already happened. The mode of action of any inhibitory receptor depends on the expression pattern of the receptor and the availability of its ligand (Rumpret et al., 2020). By providing an inhibitory signal, inhibitory receptors give additional information on the context in which an activating signal is sensed, thereby adjusting the immune response to the specific situation.

Some activating PRRs, under specific circumstances, can also demonstrate inhibitory functions. For example, TLR4 signaling from the cell membrane typically evokes proinflammatory responses, while TLR4 signaling from the endosome also triggers antiinflammatory responses (Kagan, 2012; Siegemund and Sauer, 2012). Here, we discuss the concept of inhibitory pattern recognition receptors (iPRRs). We specifically focus

on canonical inhibitory receptors that use ITIM-dependent inhibitory signaling pathways to relay their signals, resulting in inhibitory functions. We define a group of immune inhibitory receptors that recognize DAMPs, HAMPs, and PAMPs and classify these inhibitory receptors as iPRRs. We propose that, just like most activating PRRs (Gong et al., 2020), most iPRRs recognize both microbial and endogenous patterns (Fig. 2). We propose that iPRRs constitute the inhibitory counterparts of activating PRRs and provide context to the activating signals coming from activating PRRs.

iPRRs recognize DAMPs
Upon the occurrence of damaged or dying cells, different DAMPs can arise and promote inflammation, leading to tissue repair but also immunopathology (Gong et al., 2020). Multiple inhibitory receptors could potentially tune DAMP-induced inflammatory responses (Fig. 2; Arnold et al., 2013; Brewer et al., 2019; Carlin et al., 2007; Chang et al., 2014; Chen et al., 2009; Choi et al., 2011;

Conners et al., 2008; Fong et al., 2015; Gur et al., 2015; Gur et al., 2019; Jones et al., 2016; Klaile et al., 2017; Königer et al., 2016; Korotkova et al., 2008; Kumawat et al., 2019; Lebbink et al., 2009; Macauley et al., 2014; Nakayama et al., 2012; Rumpret et al., 2021a; Rumpret et al., 2021b; Simhadri et al., 2012; van Sorge et al., 2021; Virji et al., 1996; Yu et al., 2009). The sialic acid–binding Ig-like lectin (Siglec)-10–CD24 complex recognizes HMGB1, Hsp70, and Hsp90 and limits the immune response to damaged cells (Chen et al., 2009). It thereby limits harmful inflammatory responses in conditions such as sepsis (Chen et al., 2011), infection (Chen et al., 2013), and liver damage. Indeed, CD24$^{-/-}$ mice die of sublethal doses of acetaminophen-induced liver injury (Chen et al., 2009). Siglec-5 recognizes Hsp70 and delivers antiinflammatory signals to monocytes, which results in decreased production of TNFα and IL-8 in cells stimulated with LPS (Fong et al., 2015). Similarly, CD85j (leukocyte Ig-like receptor subfamily B member 1 [LILRB1]; Arnold et al., 2013) and signal inhibitory receptor on leukocytes 1 (SIRL-1; Rumpret et al., 2021a) recognize S100 proteins, another group of prototypical DAMPs. Blocking SIRL-1 enhances S100-induced release of reactive oxygen species in human neutrophils (Rumpret et al., 2021a). SIRL-1 additionally recognizes another DAMP, the antimicrobial peptide LL-37 (Rumpret et al., 2021b). LILRB3 recognizes a cytokeratin-associated protein, a cytoskeleton protein that is exposed in the extracellular environment after necrotic cell death and is recognized by the activating receptor LILRA6 (Jones et al., 2016). Thus, several iPRRs recognize DAMPs.

Die. Where? How?

Cells can die in either an immunologically silent manner (apoptosis) or an immunogenic and proinflammatory manner; the latter can be a controlled process (such as necroptosis and pyroptosis) or an uncontrolled process (necrosis). Apoptotic cells are recognized, engulfed by phagocytes, and degraded intracellularly. In contrast, membranes of cells that die via immunogenic cell death (ICD) are ruptured, and intracellular components are released into the local microenvironment, many of which are regarded as DAMPs by neighboring cells (Bedoui et al., 2020). Interestingly, the type of ICD may determine which type of DAMP is released. This is illustrated by the finding that HMGB1 release can occur after both necroptosis and pyroptosis, while release of S100, Hsp70, and Hsp90 only occurs upon necrosis and/or necroptosis, but not in the context of pyroptosis (Frank and Vince, 2019). Thus, ICD results in the release of DAMPs and sets off a chain reaction, since DAMPs themselves induce ICD in cells that recognize them. This inflammatory chain reaction can be unwanted and highly dangerous, particularly in locations with low regenerative capacity (Fig. 1). Mechanical stress, such as brain trauma, can induce both apoptosis and ICD via necrosis (Vourc'h et al., 2018). The balance between these two types of cell death in cases of mechanical stress varies between tissues and seems to shift more toward necrosis upon increased levels of stress and duration of stress (Takao et al., 2019; Valon and Levayer, 2019; Vourc'h et al., 2018). A recent review posits that a certain level of plasticity exists between apoptosis and ICD: inflammasomes, multiprotein oligomers that form intracellularly upon recognition of PAMPs or DAMPs and

usually activate ICD, can drive apoptosis when specific molecules (caspase 1 or gasdermin D) are inhibited (Bedoui et al., 2020). iPRR could provide this inhibitory signal upon recognition of DAMPs, resulting in the immediate dampening of an inflammatory chain reaction by steering the response away from ICD and toward apoptosis. Consequently, one can imagine that if inhibitory signaling occurs swiftly in sterile stress conditions, such as ischemia–reperfusion injury or trauma, inflammatory responses can be avoided. Importantly, sterile stress conditions do not always result in measurable inflammatory responses, and it is conceivable that cells in specific essential tissues do not respond to the initial release of DAMPs altogether. Since dependence on a rapid switch from ICD toward apoptosis is a risky bet for essential tissues, a more rapid alternative would be if DAMPs that bind iPRRs directly rendered the cells unresponsive.

iPRRs recognize molecules associated with homeostasis

As opposed to DAMPs, which typically are associated with danger and damage, HAMPs have previously been proposed to inhibit immune activation (Li et al., 2019; Sun et al., 2018; Wang et al., 2016). HAMPs have various properties and mechanisms of action; for example, lysophospholipids bind G protein–coupled receptors (Wang et al., 2016), and IL-35 binds cytokine receptors (Li et al., 2019). Already before the introduction of the concept of HAMPs, the guard theory of immunity was established in plants. The guard theory proposes that rather than sensing insults such as pathogens directly, the immune system recognizes the consequences of these insults for the organism. This is reflected by changes in the levels of the guard proteins, triggering immune responses (Dangl and Jones, 2001). Multiple lines of evidence suggest that the foundations of the guard theory also apply to the animal immune system (Medzhitov, 2009). Thus, HAMPs in animals and humans may be seen as a parallel to the preceding guard theory. Here, we discuss HAMPs that ligate immune inhibitory receptors.

When cells undergo apoptosis, lipids such as phosphatidylserine (PS) and phosphatidylethanolamine (PE) are exposed on the cell surface and signal tissue-resident immune cells to find and dispose of the dying cells without triggering inflammation (Arandjelovic and Ravichandran, 2015; Gordon and Plüddemann, 2018; Segawa and Nagata, 2015). PS and PE are sensed by inhibitory members of the CD300 family of immune receptors, CD300a and CD300f (Choi et al., 2011; Simhadri et al., 2012). These interactions primarily result in dampening of mast cell activation by apoptotic cells, preventing inflammatory responses (Nakahashi-Oda et al., 2012). In line with this, CD300a$^{-/-}$ mice develop exacerbated joint inflammation in an antigen-induced arthritis model (Valiate et al., 2019). In addition to apoptotic cells, viable cells can also transiently expose PS and PE, which may occur under inflammatory conditions (Arandjelovic and Ravichandran, 2015; Gong et al., 2020; Ravichandran, 2010), suggesting that additional layers of regulation may be needed to prevent phagocytosis of nonapoptotic cells. Indeed, it has been shown that CD300a/f ligation by PS and PE also negatively regulates phagocytosis of apoptotic cells (Ju et al., 2008; Simhadri et al., 2012). It is possible that a similar regulatory circuit is in place to prevent

phagocytosis of PS- or PE-bearing nonapoptotic cells. Furthermore, all host cells express diverse sialylated glycan structures, and these sialic acids are effectively a molecular pattern associated with self and homeostasis. Sialylated glycans are sensed by immune receptors of the Siglec family (reviewed in Macauley et al., 2014). Most Siglecs (human Siglec 2, 3, and 5–11) harbor an ITIM motif and are inhibitory receptors. Each Siglec exhibits preferential recognition of a different sialylated glycan. Siglecs participate in immune surveillance and provide the immune system with inhibitory signals to prevent reactivity against self. It has recently been shown that, in addition to cell surface proteins and lipids, small RNAs can be modified with glycans and tethered to the cell membrane of diverse cells under homeostatic conditions, emphasizing the role glycans play in the maintenance of homeostasis (Flynn et al., 2021). In line with this, the lack of Siglec signaling is associated with autoimmune disease. Mice double-deficient for Siglec-G and Siglec-2 spontaneously develop systemic lupus erythematosus–like systemic autoimmune disease upon aging (Jellusova et al., 2010). Other mechanisms of the host's own molecules preventing activation of the immune system have recently been demonstrated: for example, the inhibitory properties of select endogenous lipids on interactions between CD1a and TCR, effectively preventing T cell responses (Cotton et al., 2021). It remains to be determined whether similar molecules can also deliver inhibitory signals to immune cells via inhibitory receptors.

Some molecular patterns elicit activating and inhibitory signals

Several molecular patterns can be recognized by both inhibitory and activating receptors. The inhibitory receptor leukocyte-associated Ig-like receptor 1 (LAIR-1) recognizes a HAMP present in different transmembrane and extracellular matrix–associated collagens as well as collectins, leading to negative regulation of inflammatory responses, such as airway inflammation during viral infection (Kumawat et al., 2019; Lebbink et al., 2009). Collagens are also recognized by the activating receptor osteoclast-associated Ig-like receptor (OSCAR), through which they can promote inflammation (Barrow et al., 2011; Schultz et al., 2016). Further, a few Siglec receptors are activating (Macauley et al., 2014), indicating there may be instances where sialylated glycans instigate immune activation. The relative expression of activating and inhibitory receptors on immune cells in a given situation, together with other potential environmental cues, will thus determine to what extent a cell becomes activated by these molecular patterns.

iPRRs can deliver potent inhibitory signals to immune cells and attenuate or halt immune system activation. Therefore, they are often exploited by tumors to evade the immune system. For instance, many tumors highly express diverse collagens, dampening antitumor immune responses through LAIR-1 activation on immune cells (Peng et al., 2020; Rygiel et al., 2011). Similarly, various tumor types up-regulate sialylated ligands for inhibitory Siglec receptors, resulting in a dampened antitumor immune response (Fraschilla and Pillai, 2017; Jandus et al., 2014; van de Wall et al., 2020). CD155, the ligand for inhibitory receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT), is also up-regulated on tumor cells and inhibits T cell antitumor immune responses (Braun et al., 2020; Dougall et al., 2017). Up-regulation of inhibitory receptor ligands in tumor tissues thus appears to be a strategy of immune evasion in cancer.

iPRRs recognize microbial molecular patterns

Similar to how the occurrence of DAMPs does not always result in inflammation, microbial PAMPs do not always relay inflammation-promoting signals. Most microbes do not behave as either strictly pathogens or strictly commensals. Microbes with high pathogenic potential can also exist as harmless colonizers of the host, and commensal microbes can cause disease when they behave in an atypical way. Activating PRRs alone cannot differentiate between these situations, and it has thus been suggested that the immune system makes distinctions between pathogenic and nonpathogenic microbes through an integrated system of signals rather than one particular signal (Greslehner, 2020; Swiatczak et al., 2011). We argue that iPRRs may provide these additional signals.

Immune inhibitory receptors have been shown to interact with microbes, but since these interactions have been predominantly studied in experimental models of infection, it is commonly thought that iPRR–microbe interactions mediate immune evasion by the microbe (Van Avondt et al., 2015). Since most microbes are not strictly pathogens, it is reasonable to think that the interaction of microbial ligands with inhibitory receptors could contribute to symbiosis. Multiple iPRRs recognize microbial ligands (Fig. 2). *Staphylococcus aureus*, a bacterium that commonly colonizes the human skin and nasal mucosa, interacts with the mouse paired Ig-like receptor B (PIR-B, orthologue of human LILRB3) through LTA, thereby limiting proinflammatory cytokine production. Indeed, PIR-B$^{-/-}$ mice infected with *S. aureus* show decreased survival compared with wild-type mice (Nakayama et al., 2012). LTA is a PAMP and an essential component of the cell wall universally expressed not only by *S. aureus*, but also by other related, less pathogenic species. The inhibitory receptor PIR-B/LILRB3 could thus regulate the host interaction with *S. aureus* in a noninflammatory context through recognition of PAMPs.

As discussed above, endogenous sialic acids are a molecular pattern associated with self and homeostasis, and they interact with different inhibitory Siglec receptors. Sialic acids present on the surface of group B streptococcus (GBS) likewise interact with inhibitory Siglecs (Carlin et al., 2007; Chang et al., 2014). The sialic acid is common to all GBSs, which is not a strict pathogen but rather an opportunist. CD33 Siglecs are expressed in skin-resident Langerhans cells, which could allow for interaction between Langerhans cells and GBS, resulting in an inhibitory signal and thus promoting the colonizing lifestyle of GBS. Other inhibitory receptors interacting with bacteria are SIRL-1, which recognizes staphylococcal phenol-soluble modulins (Rumpret et al., 2021b), and TIGIT, which recognizes a ligand expressed by the oral commensal bacterium *Fusobacterium nucleatum* (Gur et al., 2015). The functional roles of these interactions are yet to be fully explored.

A particularly prominent binder of microbial ligands is the inhibitory receptor carcinoembryonic antigen-related

Table 1. **Overview of different properties of iPRRs**

iPRR	iPRR expression	iPRR structure	Signaling pathway	Endogenous ligand	Endogenous ligand expression	Microbial ligand	Activating receptor for the same ligand
CD300a/f	Broad on immune cells, upregulated on activation	Ig-like	ITIM	PS, PE	Exposed in programmed cell death	—	Tim4
CEACAM-1	Broad on immune, epithelial, and endothelial cells	Ig-like	ITIM	CEACAM1 and other CEACAMs	Constitutive	Ig fold proteins	Other CEACAMs
LAIR-1	Broad on immune cells; on activation, upregulated on neutrophils and downregulated on T cells	Ig-like	ITIM	Collagen	Constitutive	—	OSCAR
LILRB1 (CD85j)	Neutrophil, monocyte, dendritic cell, and NK cell, upregulated on activation	Ig-like	ITIM	S100 proteins	Upon cell damage	—	TLR4, RAGE
LILRB3 (CD85a)	Neutrophil, monocyte, dendritic cell	Ig-like	ITIM	Unknown cytokeratin-associated ligand	Upon cell damage	Unknown in *S. aureus* (LTA shown for mice ortholog PIR-B)	TLR2/6
PVR	Dendritic cell, upregulated on activation	Ig-like	ITIM	Nectin-3	Constitutive	Poliovirus	—
Siglec 2, 3, 5–11	Broad on immune cells, differs per receptor	Ig-like	ITIM	Sialic acids	Constitutive	Sialic acids	Siglec 14–16
Siglec 2, 3, 5–11	Broad on immune cells, differs per receptor	Ig-like	ITIM	Hsp70	Upon cell damage	—	TLR4, RAGE
Siglec 10	B cell, eosinophil, monocyte	Ig-like	ITIM	HMGB1, Hsp90	Upon cell damage	—	TLR4, RAGE
SIRL-1	Neutrophil, monocyte, downregulated on activation	Ig-like	ITIM	LL-37, S100 proteins	Upon cell damage and immune activation	Phenol-soluble modulins of *Staphylococcus*	TLR4, RAGE, FPR2
TIGIT	T cell, NK cell, upregulated on activation	Ig-like	ITIM	DNAM-1, TIGIT	TIGIT upregulated on activation	Unknown in *F. nucleatum*	DNAM-1

OSCAR, osteoclast-associated Ig-like receptor; PVR, poliovirus receptor; RAGE, receptor for advanced glycation end products.

cell adhesion molecule 1 (CEACAM1). On immune cells, CEACAM1 is restrictively expressed on activated cells, whereas it is constitutively expressed by epithelial cells (Gray-Owen and Blumberg, 2006; Huang et al., 2015). It binds many different microbial ligands, such as bacterial Dr adhesins of *Escherichia coli* (Korotkova et al., 2008), the Opa protein of *Neisseria meningitidis*, *Neisseria gonorrhoeae* (Virji et al., 1996) and commensal *Neisseria* species (Toleman et al., 2001), adhesin UspA1 of *Moraxella catarrhalis* (Conners et al., 2008), the HopQ adhesin of *Helicobacter pylori* (Königer et al., 2016), CbpF adhesion of *Fusobacterium sp.* (Brewer et al., 2019; Gur et al., 2019), the streptococcal β protein (van Sorge et al., 2021), and an unidentified ligand in the fungus *Candida sp.* (Klaile et al., 2017). Although most of these microbes can be pathogenic, they do not always cause disease. Moreover, the absence of CEACAM1 has been shown in mouse models to predispose to colitis (Jin et al., 2016; Nagaishi et al., 2006). Together, these data indicate that CEACAM1 may have a tolerizing function in host–microbe interactions rather than serving only as a means for immune evasion.

Concluding remarks and future perspectives

Here, we define a group of inhibitory receptors that can be classified as iPRRs. We argue that iPRRs, like their activating counterparts, recognize molecular patterns (Table 1; Akira et al., 2006; Alvarez et al., 2008; An and Brodsky, 2016; Angata et al., 2002; Arakawa et al., 2018; Arnold et al., 2013; Brewer et al., 2019; Brown and Crocker, 2016; Carlin et al., 2007; Chang et al., 2014; Chen et al., 2009; Choi et al., 2011; Conners et al., 2008; Dougall et al., 2017; Fong et al., 2015; Gray-Owen and Blumberg, 2006; Gur et al., 2015; Gur et al., 2019; Han et al., 2005; Jones et al., 2016; Klaile et al., 2017; Königer et al., 2016; Korotkova et al., 2008; Kretschmer et al., 2010; Kumawat et al., 2019; Lebbink et al., 2009; Lewis Marffy and McCarthy, 2020; Liu et al., 2014; Macauley et al., 2014; Nakayama et al., 2012; Nakayama et al., 2007; Nuñez et al., 2018; Pende et al., 2006; Pérez-Oliva et al., 2011; Prantner et al., 2020; Rumpret et al., 2021a; Rumpret et al., 2021b; Segawa and Nagata, 2015; Simhadri et al., 2012; Sims et al., 2010; Steevels et al., 2013; van Sorge et al., 2021; Virji et al., 1996; Young et al., 2008; Yu et al., 2009; Zenarruzabeitia et al., 2015). This recognition provides context- and location-dependent signals to help shape the immune response. We
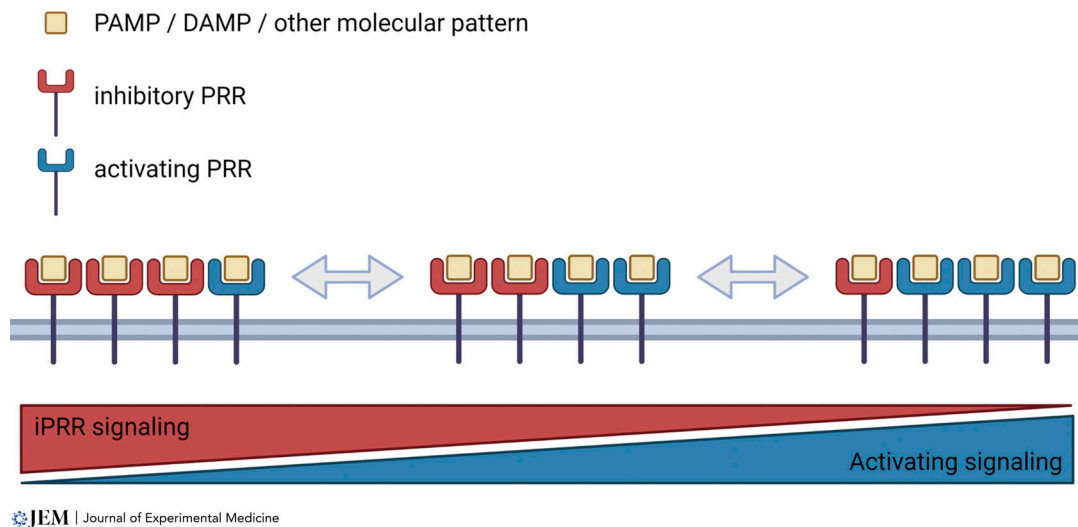
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Figure 3. **The integration of activating and inhibitory signals determines the outcome of the immune response.** When damage or a dangerous microbe should not be tolerated, DAMPs and PAMPs signal through activating PRRs to mount an immune response. However, when it is more beneficial for the host to tolerate damage or a harmless microbe, then the same DAMP or PAMP, or a different pattern, can concomitantly signal an iPRR to inhibit the immune response. The relative expression of PRRs and iPRRs and their respective ligands determine the strength of the resulting immune response.

indicate that most of the iPRRs discussed here are able to recognize both endogenous and microbial patterns (Fig. 2). The relative expression of activating and inhibitory PRRs and the integration of their signals ultimately determines the strength of an immune response to microbes or damage. This allows a differential response to tissue damage in different organs, depending on their susceptibility to immunopathology (Fig. 1). For example, in tissues that have low regenerative capacity, such as the brain, increased expression of iPRRs could provide a higher activation threshold and prevent the release of DAMPs that leads to inflammation and further tissue damage (Ashour et al., 2021). We also point out that endogenous patterns can signal "safety" via iPRRs to ensure that commonly occurring events such as apoptosis do not trigger the immune system. Similarly, there may be microbial patterns ensuring that harmless microbes colonizing the host do not bring about inflammatory responses (Fig. 3). For example, in the blood, microbial patterns such as LTA are recognized by activating PRRs. In contrast, in other anatomic locations such as the skin, iPRRs could also signal in response to these patterns, abrogating their potential to trigger inflammatory responses. We argue that the interactions between iPRRs and their microbial ligands may thus be vital for establishing and maintaining commensal–host homeostasis and suggest that studies in this direction are needed to examine this hypothesis. Further exploration of possible additional iPRRs, their ligands, and their expression patterns will provide a better understanding of the interactions of the host with its microbiota and the contextual regulation of septic and sterile inflammation.

Finally, iPRRs can be exploited to treat or prevent disease. The increased understanding of the function of inhibitory receptors has led to significant advances in the treatment of cancer. PD-1 and CTLA-4 have proven their potential as therapeutic targets on T cells for cancer immunotherapy (Ribas and Wolchok, 2018). Innate cells such as NK cells, innate lymphoid cells, and different myeloid cell types are also important in anticancer immune responses. These cells can directly contribute to tumor removal and additionally modulate antitumor T cell responses by steering T cell activation. Different iPRRs expressed on these cells, such as TIGIT and CD96, are already being explored as additional therapeutic targets (Dougall et al., 2017). With an increased understanding of the properties of iPRRs and their ligands, we expect that more of these receptors will be used as targets for immunotherapy.

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