CHAPTER 1

Macrophage Pattern Recognition Receptors in Immunity, Homeostasis and Self Tolerance

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Abstract

Macrophages, a major component of innate immune defence, express a large repertoire of different classes of pattern recognition receptors and other surface antigens which determine the immunologic and homeostatic potential of these versatile cells. In the light of present knowledge of macrophage surface antigens, we discuss self versus nonself recognition, microbicidal effector functions and self tolerance in the innate immune system.

Introduction

The common basic features of any functional immune systems are: (i) ability to distinguish self tissues from microbial invaders (self vs nonself recognition), (ii) mount an appropriate effector response to kill or contain microbial infection, and perhaps most importantly, (iii) spare the host tissues from potentially hazardous effector responses (self tolerance). All known immune systems, however primitive or advanced, show these three basic characteristics.[1] However, the ability of the immune system to recognize and respond to foreign materials or tolerate self components is not absolute; these functions operate robustly within a given range, as normal physiology, beyond which dysfunction leads to immune pathology. Susceptibility to infection, immunopathology and autoimmunity are probably extreme examples in a spectrum of immune failure.

The molecular basis for immune recognition, response and tolerance is relatively well-studied in adaptive immunity of vertebrates, but such research was neglected in innate immunity until recently, despite the fact that most species rely solely on innate immunity to achieve these core immune functions. Innate immunity lacks most of the basic molecular machinery employed by the adaptive system such as somatically rearranged high affinity antigen receptors used by lymphocytes and thymic education of T cells for central tolerance, indicating the presence of a fundamentally different mechanism in innate immunity. The first major conceptual breakthrough came when Janeway proposed that cells of the innate immune system express a large repertoire of germ-line encoded receptors which recognize invariant molecular structures on pathogens, which are essential and unique to pathogens and not present in the host. He coined the term pathogen associated molecular patterns (PAMPs) for such molecular structures, recognised by pattern recognition receptors (PRR).[2,3] Since Janeway's proposal a large number of PRRs have been identified. Similar to adaptive Ag recognition receptors, innate PRRs can be defined as humoral and cell associated. Cellular

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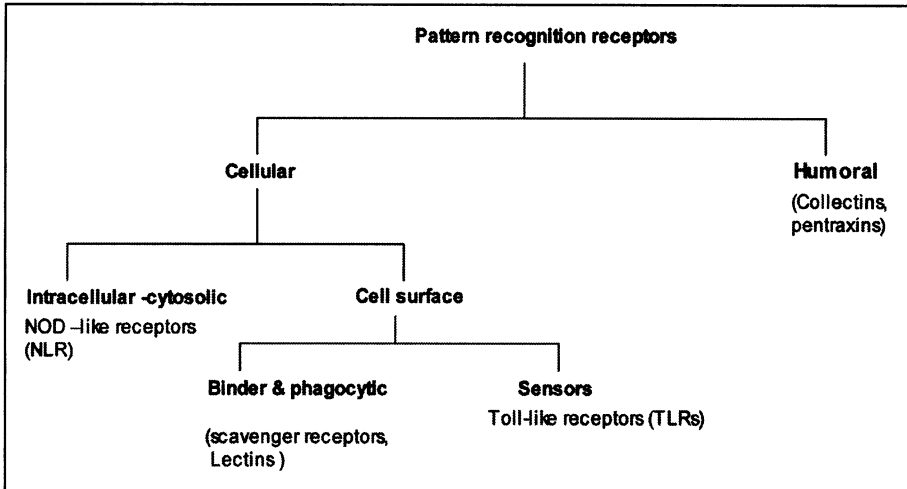
Figure 1. Schematic representation of different classes of pattern recognition receptors.

PRRs are further subdivided into intracellular or cell surface molecules. Humoral PRRs generally recognise pathogens from various body fluids and form aggregates which are subsequently cleared by phagocytes. Apart from this opsonising ability they also have many immunomodulatory properties. Cell surface PRRs are either phagocytic/endocytic or sensor in nature. Phagocytic receptors bind and internalise ligands directly and display temperature dependent, saturable and inhibitable ligand binding kinetics of classical receptors. On the other hand sensors do not bind or internalise ligand directly, but recognise PAMPs and induce a proinflammatory signalling cascade which leads to many antimicrobial effector responses. It is important to note that many intracellular PRRs are also sensing molecules.[4] A schematic diagram of different classes of PRRs and selected examples are presented in Figure 1. There is recent evidence that components of the cellular and humoral arms of the innate immune system collaborate to induce and maintain host defence.[5,6]

    Although amendments have been recently proposed to the original concept of pattern recognition, this remains fundamental to our present understanding of innate immunity. "Molecular patterns" are not restricted to pathogens, but are also expressed by commensals; it has been argued that microbial ligands should be characterised molecularly, in preference to introducing the term PAMP.[7] Although not clearly stated, it could be extrapolated from Janeway's proposal that self tolerance is achieved in innate immunity through "ignorance" as PRRs only recognize microbial molecules. This is in contrast to adaptive immunity where tolerance is achieved by "education". This theory of ignorance is challenged by recent observations that many PRRs recognize modified host molecules (generated during normal or aberrant metabolism) as well as naturally occurring host molecules, other than microbial structures.[8] It is conceivable that during evolution multipurpose PRRs were selected to recognize microbial molecules to counter infectious challenges, modified host molecules for clearing, homeostasis and natural host molecules for immunomodulation, thus minimizing the genetic resources invested in immunity.

    In this chapter we will discuss how PRRs differentially recognize microbial, modified host molecules as well as natural host molecules using examples from two major classes of PRRs, class A scavenger receptors and C type lectin families. We also speculate how tolerance is achieved in innate immunity.
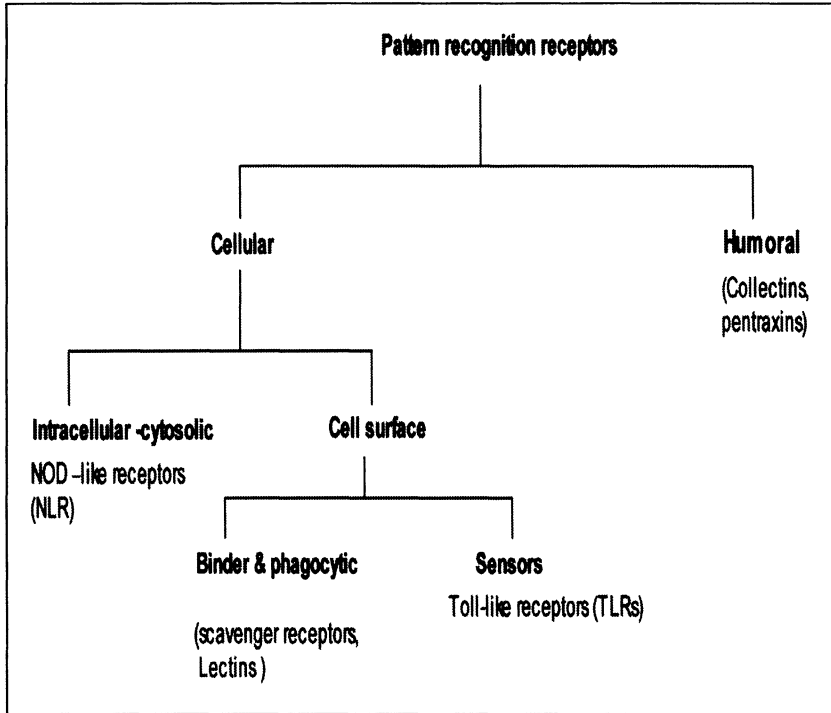
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                              Pattern recognition receptors
                                          |
                  ┌───────────────────────┴───────────────────────────┐
               Cellular                                             Humoral
                  |                                                (Collectins,
                  |                                                 pentraxins)
         ┌────────┴─────────────────────┐
 Intracellular -cytosolic          Cell surface
 NOD -like receptors                    |
 (NLR)                          ┌────────┴──────────────┐
                         Binder & phagocytic         Sensors
                                                Toll-like receptors (TLRs)
                         (scavenger receptors,
                         Lectins)
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Figure 2. Different members of the class A scavenger receptor family. The scavenger receptor AI/II (SR-A), macrophage receptor with collgenous structure (MARCO) and scavenger receptor with C-type lectin-I/II (SRCL) all are three members of the class A SR family. Both SR-A and SRCL have two functional isforms, where the C terminus of SR-AII and SRCL-II are truncated. SR-A was the first member identified in this family, subsequently MARCO and SRCL were included in this family due to their structural similarities with SR-A. SR-A is a Type II trans-membrane glycoprotein which shows multi-domain protein structure with a short cytoplasmic tail, transmembrane region, followed by an extracellular spacer region, an α helical coiled coil region, a collagenous domain and a C terminal scavenger receptor cysteine-rich (SRCR) domain. Although MARCO and SRCL share a similar domain organization to that of SR-AI, the only differences are that MARCO lacks an α_helical coiled coil domain and possesses a longer collagenous domain; in the case of SRCL-I, the SRCR domain is replaced by a C-type lectin domain. Functionally, all three receptors show overlapping ligand binding properties and contribute to varied functions.

The Scavenger Receptor Family

The scavenger receptors were functionally defined by Brown and Goldstein for their ability to bind and internalise modified low density lipoprotein (mLDL) such as oxidised LDL (Ox-LDL), acetylated LDL (Ac-LDL), but not native LDL.[9] Subsequently a variety of artificial and natural polyanionic ligands including many micro-organisms and apoptotic cells were identified as ligands for SRs. After Brown and Goldstein's first proposal a large number of unrelated distinct gene products were identified which bind mLDL. Krieger and colleagues classified these molecules (classes A-F) according to their similarities in multi-domain protein structure.[10] Recently several new molecules have been identified and two new classes (G and H) added to this list to accommodate novel structural features, totalling 8 independent structural classes of SR which possess common functional criteria.[11] In this chapter we will restrict our discussion to class A SR family (Fig. 2 and refer to Table 1).

Table 1. Class A scavenger receptor recognition of endogenous and exogenous ligands

Receptor	Microbial Ligand	Refs	Endogenous Ligand	Refs	Modified Self Ligand	Refs
SR-A	LPS and LTA	15	Unidentified protein ligand in serum	25	β amyloid protein	23
			Activated B cells	26	Apoptotic cells	38
					Ox-LDL and Ac-LDL	9
					AGE modified protein	24
MARCO	LPS	39	UGRP-1	34	Ac-LDL	40
SRCL-I	G⁺, G⁻ bacteria, Yeast	35,36	T and Tn antigen	37	Ox-LDL	35,36

Class A Scavenger Receptors

SR-A was the first molecule in this class to be cloned. Three alternatively spliced variants (SR-AI/II and III) of the same gene have been identified which are collectively called SR-A. Among these three splice variants SR-AIII is non functional and trapped in the endoplasmic reticulum. So far, no functional difference has been observed between SR-AI and II. SR-A is a Type II trimeric transmembrane glycoprotein molecule with a cytoplasmic tail, transmembrane region, followed by an extracellular spacer region, an α helical coiled coil region, a collagenous domain and a C terminal scavenger receptor cysteine-rich (SRCR) domain. The SRCR domain is absent in SR-AII and III. The collagenous domain is responsible for ligand binding, but the cytoplasmic tail is required for endocytosis and phagocytosis of ligand or adhesion to ligand-rich substrata.[12] Macrophage receptor with collagenous structure (MARCO) and scavenger receptor with C type lectin I (SRCL-I) are the other two members of the class A SR family which share a similar domain organization to that of SR-AI. The only differences are that MARCO lacks an α helical coiled coil domain and possesses a longer collagenous domain; in the case of SRCL-I, the SRCR domain is replaced by a C-type lectin domain. It has been proposed that similarly to SR-AI, SRCL-I binds Ox-LDL through its collagenous region, but exhibits additional sugar binding properties through the C-type lectin domain. In contrast, MARCO may recognise ligands through its SRCR region.[13,14]

SR-A (SR-AI/II)

The first evidence that SR-A can recognise nonself microbial components came with the observation that SR-A could bind the lipid-A portion of lipopolysaccharide (LPS) and lipoteichoic acid (LTA).[15] Furthermore, different LTA structures showed differential specificity depending on their exposed negative charge available to SR-A.[16] Another bacterial component CpG DNA, has also been reported to be recognised by SR-A, but its immunostimulatory effect is independent of SR-A.[17] Finally, Dunne et al confirmed that SR-A also binds intact Gram-positive and negative organisms.[18] In a direct binding assay, use of different strains of *Escherichia coli* and *Staphylococcus aureus* and primary macrophages (Mφ) from wild type (WT) and SR-A⁻/⁻ mice confirmed that the contribution of SR-A to bacterial recognition depended on the source of Mφ and the strain of bacteria.[19] Several in vivo infection models showed that SR-A⁻/⁻ animals are more susceptible to *Listeria monocytogenes* and *S. aureus* infection, underscoring the importance of SR-A in antibacterial host defence.[20,21] Screening of several pathogenic and nonpathogenic bacterial strains in an in vitro binding assay showed that SR-A contributes to the majority of *Neisserial* recognition by Mφ, but the contribution is minimal to recognition of *Haemophilus sp*, indicating strain-specific recognition (Peiser & Gordon, unpublished observation). Furthermore, although LPS has been shown to be a ligand for SR-A, use of an LPS deficient mutant strain

confirmed that SR-A mediated recognition of *Neisseria meningitidis* is LPS-independent, indicating the presence of nonLPS ligands for SR-A.[22] Recently we have identified several surface proteins on *N. meningitidis* which are ligands for SR-A, providing evidence for unmodified protein ligands for SR-A (Peiser and Gordon submitted).

As mentioned earlier, SR-A was first identified by its ability to bind mLDL. Subsequently, several other modified self molecules were identified as SR-A ligands which are generated during normal or aberrant metabolism. SR-A recognises β amyloid proteins, a hallmark of Alzheimer's disease, and contributes to the inflammatory nature of this disease by recruitment and adhesion of Mφ. Similarly, SR-A contributes to inflammatory pathology by recognising advanced glycation end products (AGE) generated during diabetes. In contrast, SR-A contributes to phagocytosis of apoptotic cells inducing a profound anti-inflammatory response.[23,24]

Fraser et al first described the presence of a natural ligand for SR-A in human and bovine serum which allows divalent cation-independent adhesion of Mφ to tissue- culture plastic through SR-A.[25] Presently our group is involved in identifying the chemical nature and physiological role of this serum ligand. Similarly, another unidentified natural ligand for SR-A has been reported on activated B cells, but its physiological relevance is unknown.[26]

MARCO

Functional binding studies confirmed that SR-A and MARCO not only share very similar structural features, but also show similar ligand binding properties. Similarly to SR-A, MARCO also binds several Gram-positive and negative organisms or their isolated products such as LPS or CpG DNA.[27] Infectious challenge with the lung pathogen *Streptococcus pneumoniae* confirmed that MARCO^{−/−} mice display an impaired ability to clear pneumococcal infection, resulting in increased pulmonary inflammation and reduced survival, confirming a role of MARCO in antibacterial protection.[28] Recently we have reported that like SR-A, MARCO also recognises *Neisseria* independent of LPS.[29] Furthermore, we identified several *Neisserial* surface proteins as potential nonLPS ligands for MARCO, distinct from those that bind SR-A (Mukhopadhyay & Gordon, unpublished observation). Other than microbial pathogens, MARCO also binds and protects the host from a range of nonself environmental pollutants such as TiO_2 and asbestos.[30] MARCO has been reported to bind modified self ligands such as Ox-LDL and Ac-LDL. MARCO expression is induced in murine atherosclerotic plaques, but its exact role in the pathogenesis of atherosclerosis remains to be determined.[31] The presence of natural or self ligand(s) for MARCO has been reported on subsets of splenic marginal zone B cells. Blockade of this cell-cell interaction confirmed that it is critical for development and retention of the marginal zone microarchitecture in rodent spleen.[32] Similarly, MARCO^{−/−} animals showed defects in splenic microarchitecture, with significant immunological consequences.[33] Uteroglobin related protein -1 (UGRP-I), a secreted protein expressed by lung clara cells, has been shown to be another endogenous ligand for MARCO. UGRP-I also binds to bacteria and therefore may act as an opsonin which increases MARCO-mediated clearance of bacteria.[34]

SRCL-I/ CLP-I

Recently two groups independently cloned a novel member of the class A SR family from a human placental cDNA library, designated as SRCL-I (scavenger receptor with C-type lectin) and CLP-I (Collectin from placenta-1), respectively. As mentioned earlier, this molecule differs from SR-AI by its C terminal C-type lectin domain in place of a SRCR domain. One group also identified a C terminal truncated form of this molecule which lacks the C-type lectin domain and displays a very similar structure to that of SR-AII. These studies showed that SRCL-I transfectants bind Gram-positive and negative bacteria, as well as yeast and Ox-LDL in a polyanion sensitive manner. Fungal recognition by SRCL-I is not observed with other class A SR family molecules and possibly occurs through the lectin domain.[35,36] The C-type lectin domain showed specificity for GalNac type glycoconjugates which is inhibitable by free GalNac, L-D-fucose and D-galactose. SRCL-I has also been shown to bind T and Tn antigens, two carcinoma associated autoantigens which display distinct modified glycosylation.[37]
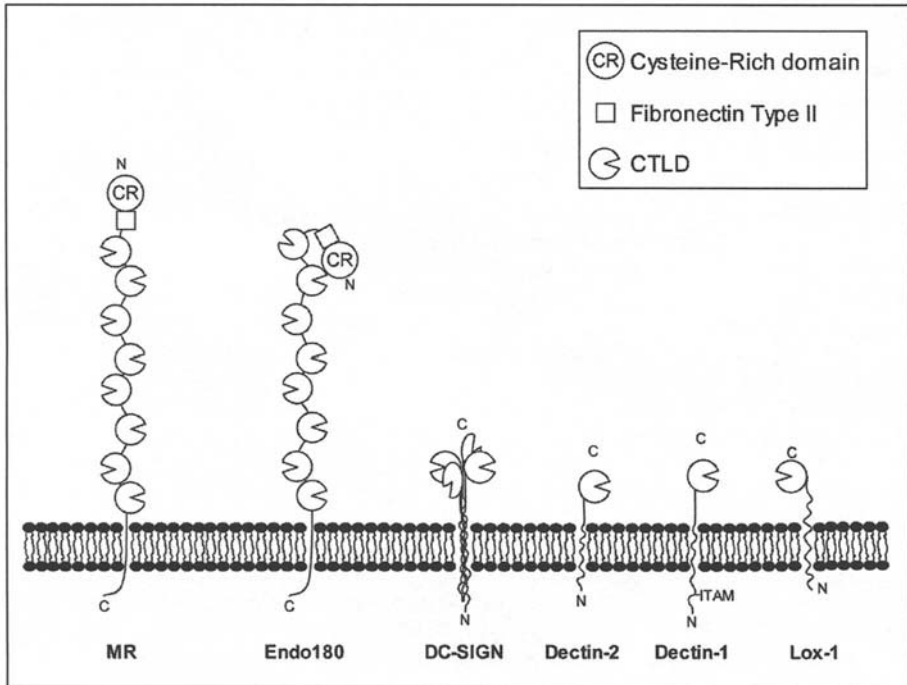
Figure 3. C-type lectin receptors. The C-type lectin receptor (CLR) family is made up of a wide range of receptors that are defined in part by their ability to bind carbohydrate molecules. Some C-type lectins contain multiple lectin domains (Mannose receptor and Endo180) while others contain a single lectin domain (Lox-1, Dectin-1). In the case of Lox-1 and Dectin-1, the lectin domain is called NK like C-type lectin like (NKCL) domain, the major difference between NKCL and the classical C-type lectin domain is the sugar binding in the former is calcium independent. The mannose receptor and Endo180 is expressed by most macrophages, dendritic cells (DCs), tracheal smooth muscle cells and endothelial cells. Endo180 is predominantly expressed by fibroblasts, endothelial cells and macrophages. DC-SIGN is highly expressed by mature and immature DCs and by sub-populations of macrophages in the lung and placenta. Dectin-1 and Dectin-2 are predominantly expressed on myeloid cells, including macrophages, DCs and neutrophils. Lox-1 is expressed on vascular endothelial cells, smooth muscle cells, fibroblasts, platelets and macrophages.[4,92]

C-Type Lectin Receptors

The C-type lectin receptor (CLR) family is made up of a wide range of receptors that are defined in part by their ability to bind carbohydrate molecules (Fig. 3).[4] They can be divided into three groups, (1) the C-type lectins containing a single carbohydrate recognition domain (CRD), (2) the C-type lectins containing multiple CRDs and (3) the NK-like C-type lectin-like receptors (NKCL) which have a single CRD. The classical C-type lectins require calcium for binding, however the NKCL receptors differ from the other two groups in that their C-type lectin domains (CTLD) lack the residues involved in calcium binding. Members of the C-type lectins with a single CRD are Type II membrane receptors and include DC-SIGN and Dectin-2. C-type lectins containing multiple CRDs are Type I membrane receptors and include the mannose receptor (MR), Endo180, DEC-205 and the phospholipase A$_2$ receptor.[41] The Type II membrane receptors termed NK-like C-type lectin-like receptors include Dectin-1, CD69 and LOX-1 (reviewed in ref. 4). Most of these receptors recognise both endogenous and exogenous molecules, self and nonself ligands. A few examples of CLRs and their binding properties will be discussed in the following section.

C-Type Lectins with a Single CRD

This group of receptors is made up of DC-SIGN and related molecules. DC-SIGN (CD209) was originally described to be involved in the adhesion of T-cells to dendritic cells via the intercellular adhesion molecule 3 (ICAM-3) and therefore the receptor was designated dendritic cell-specific ICAM-grabbing nonintegrin.[42] The receptor has since also been shown to play a role in DC migration via ICAM-2, a molecule that is highly expressed on vascular and lymphoid endothelium.[43] DC-SIGN is a tetrameric endocytic receptor consisting of a single CTDL, a stalk region, a transmembrane domain and a cytoplasmic tail containing an internalisation motif.[4] It generally recognises N-linked high mannose structures as well as fucose-containing glycans, but also discriminates between ligands on the basis of secondary binding sites.[44] The key to selective interaction with pathogens may be in the close proximity of the four CRDs which bind closely spaced glycans, as clusters of either mannose-type or fucose-type ligands are not common in endogenous molecules. This receptor has been shown to be involved in the recognition of various pathogens including viruses such as HIV-1, HCMV, Hepatitis C, Dengue and Ebola, as well as *Mycobacterium tuberculosis, Candida albicans, Leishmania mexicana, Helicobacter pylori* and *Schistosoma mansoni* (Table 2).[45,46] The carbohydrate ligand on *H. pylori* and *S. mansoni* was found to be the nonsialylated Lewis^x antigen.[45,47] Dengue virus that infects dendritic cells has been shown to utilise DC-SIGN for enhanced cell entry.[48] Interestingly, an association between a variant in the *CD209* promoter and severity of dengue disease was shown recently.[49] In some cases the pathogens modulate the immune response by binding to DC-SIGN and examples of this are HIV-1 and *M. tuberculosis*.[50] HIV-1 exploits the antigen presenting properties of DC-SIGN to gain access to T-cells that are the primary target of the virus. The binding of mycobacterial lipoarabinomannan to DC-SIGN blocks DC maturation and triggers inhibitory signals that allow this bacterium to evade the immune response.[51] Dendritic cells play a pivotal role in antitumor responses where DC-SIGN interacts with colorectal cancer cells via Lewis^x carbohydrate moieties on carcinoembryonic antigen produced by the cancer cells during malignant transformation.[52] Recently it has been shown that DCs interact with neutrophils via DC-SIGN-mediated binding to the nonsialylated Lewis^x antigen on Mac-1 of these cells.[53] Since activated neutrophils induce DC maturation which in turn triggers the T-cell response, this indicates that neutrophils may contribute to adaptive immune responses via their interaction with DCs, providing a cellular link between innate and adaptive immunity.

C-Type Lectins with Multiple CRDs

The structure of these receptors includes an N-terminal cysteine-rich domain, a domain containing fibronectin Type II repeats, multiple extracellular CTLDs, a transmembrane domain and a short cytoplasmic tail.[41] The best characterised receptor in this group is the mannose receptor (MR) (CD206). This receptor is a 180-kDa Ca^{2+}-dependent lectin that functions as an endocytic receptor and has been shown to bind bacteria, viruses and yeasts (Table 2).[54] MR specifically binds terminal mannose, fucose, N-acetylglucosamine or glucose residues which allow it to distinguish nonself from self as these moieties are commonly found on microorganisms, but not in terminal positions on mammalian cell surface oligosaccharides or serum glycoproteins.[55] On alveolar macrophages, for example, the mannose receptor has been identified as a pattern recognition receptor capable of NF-κB activation in response to the fungus *Pneumocystis*.[56] The ligand on *Pneumocystis carinii* mediating interaction with the mannose receptor was shown to be the major mannose-rich surface antigen complex termed glycoprotein A (gpA).[57] This receptor has also been implicated in nonopsonic binding of another pathogenic fungus, *C. albicans*, most likely via mannose residues on the fungal surface.[58,59] The cysteine-rich domain has been shown to bind endogenous glycoproteins via their sulphated N-acetylgalactosamine or galactose moieties[60] and this receptor has been implicated in the clearance of serum glycoproteins to maintain homeostasis.[61] On dendritic cells, the mannose receptor plays a role in binding to MUC1, an aberrantly glycosylated membrane protein that is highly expressed on tumour cells and is released into the circulation.[62]

Table 2. C-type lectin recognition of endogenous and exogenous ligands

Receptor	Microbial Ligand	Ref.	Endogenous Ligand	Ref.	Modified Self Ligand	Ref.
DC-SIGN	HIV-1 Envelope glycoprotein gp120	68	Intercellular adhesion molecule (ICAM)-3	42	Tumor-associated carcino-embryonic antigen	52
	Hepatitis C virus envelope glycoproteins E1 and E2	69	ICAM-2	43		
	Dengue virus	48	β2-integrin Mac-1 on neutrophils	53		
	Marburg virus glycoprotein	70				
	Severe acute respiratory syndrome coronavirus S protein	70				
	Helicobacter pylori LPS containing Lewis^x antigen	45				
	Schistosoma mansoni glycan antigen (Lewis^x) of soluble egg antigen	47				
	Leishmania mexicana mannose capped surface lipophosphoglycan	45				
	Mycobacterium tuberculosis lipoarabinomannan	51				
	Candida albicans	71				
	Aspergillus fumigatus	72				
SIGNR1	*Streptococcus pneumoniae* capsular polysaccharide	73	ICAM-2	43	NR	
	Candida albicans	74	ICAM-3	42		
	HIV-1 gp120	75				

Table 2. Continued

Receptor	Microbial Ligand	Ref.	Endogenous Ligand	Ref.	Modified Self Ligand	Ref.
Dectin-2	*Mycobacterium tuberculosis*	50	ICAM-3	42	NR	62
	HIV-1	50				
Mannose receptor	*Pneumocystis carinii* Glycoprotein A	57	CD45	76	MUC1	
	Candida albicans	58	Sialoadhesin	76		
	Klebsiella pneumoniae lipopolysaccharide	77	Lysosomal acid phosphatase	78		
	Streptococcus pneumoniae Capsular polysaccharide	77	myeloperoxidase	79		
	Influenza A virus	80	Serum glycoproteins	61		
	HIV-1	81	Lutropin hormone	82		
Endo180	NR		Collagen	83	Denatured collagen	4
Dectin-1	*Candida albicans* β-glucan	63	T-cell ligand	67	NR	
	Saccharomyces cerevisiae β-glucan	63				
	Pneumocystis carinii	66				
LOX-1	*Staphylococcus aureus*	84	Activated platelets	85	OxLDL	86
	Escherichia coli	84	Hsp70	87	Apoptotic cells	85

* NR: not reported.

NK-Like C-Type Lectin-Like Receptors

These receptors typically possess a single extracellular carbohydrate binding domain (CTLD), a stalk region, a transmembrane domain and a cytoplasmic tail with or without signalling motifs.[4] Some receptors in this family contain cysteine residues in the stalk region which are involved in homo- or heterodimerization. Dectin-1 is a small (~28 kDa) Type-II membrane receptor with a single extracellular C-type lectin-like domain and a cytoplasmic domain with a tyrosine-based activation motif.[63,64] Carbohydrate recognition is independent of calcium. It recognises a variety of β-1,3-linked and β-1,6-linked glucans and thus binds and promotes phagocytosis of yeasts such as *Saccharomyces cerevisiae* and *C. albicans*.[63,65] In alveolar macrophages, Dectin-1 has been shown to bind the fungus *P. carinii*.[66] In contrast to the mannose receptor, it does not recognise monosaccharides or carbohydrates with different linkages. Dectin-1 has also been shown to interact with an endogenous ligand on activated T-cells, although the identity of this ligand is as yet unknown.[67]

Self Tolerance in Innate Immunity

In recent years there has been significant progress in the field of innate recognition and antimicrobial host defence. However, our knowledge concerning induction of tolerance in the innate immune system is still rudimentary and the role of PRRs in tolerance induction is not clear. It is proposed that microbes express ligands for both phagocytic and sensing PRRs which simultaneously engage these two classes of receptors and induce full scale antimicrobial responses. However, phagocytic receptors possibly recognise natural or modified self molecules in the absence of TLR stimulation, resulting in a tolerogenic outcome. Recognition of modified self molecules by phagocytic receptors can also lead to inflammatory responses such as recognition of mLDL or β amyloid protein by SR-A. It is conceivable that in such aberrant metabolic conditions, TLR agonists are also produced which promote a dual signal through SR-A and TLR. Other than PRR mediated recognition several other possible mechanisms for tolerance induction have been proposed in innate immunity.

Our first mechanistic insight concerning tolerance induction in the innate system came from studies on activatory and inhibitory natural killer (NK) cell receptors. NK cells express a range of ITAM containing inhibitory receptors which recognise MHC class I molecules which are present in all nucleated cells of the body as a marker of self, sparing them from killing. On the other hand, if MHC-I expression is absent or reduced, as in the case of viral infection or tumour cells, NK cells recognise them as foreign. However, "missing self" alone does not determine the target cell killing and virus-infected or tumour cells also express ligands for many activatory receptors present on NK cells, which initiate the killing machinery. Therefore absence of MHC-I as a self marker and presence of ligands for activatory NK cell receptors together act as a switch for cytotoxic activity of NK cells.[88]

Inhibitory receptor-mediated self tolerance is also observed in the Mφ system. SIRP-α (CD172a) is a predominantly myeloid restricted molecule of the immunoglobulin superfamily (IGSF), whereas its ligand CD47 is more broadly expressed, including on myeloid cells. CD172a contains three extracellular Ig-like domains; its intracellular domain contains several tyrosines and has been shown to interact with the tyrosine phosphatases SHP1 and SHP2. This inhibits Mφ activation, such as the response to growth factors or phagocytosis via Fc or complement receptors. Recently Oldenborg et al showed that CD47^{-/-} red blood cells are rapidly cleared by splenic red pulp Mφ after infusion in WT animals. CD47 expression on WT RBC prevents such elimination by binding to the inhibitory molecule, CD172a. Thus Mφ rely on the presence or absence of CD47 to distinguish self from foreign.[89]

CD200 and CD200R are both members of the IGSF and contain two Ig domains each in their extracellular region. CD200 has a very short cytoplasmic domain and is unable to signal. In contrast, CD200R contains several tyrosine phosphorylation sites in its relatively longer cytoplasmic tail. CD200 is reported to be expressed by a broad range of cells including neurones, but not by myeloid cells. On the other hand CD200R expression is restricted to myeloid cells,

particularly Mφ. Interaction between CD200 and CD200R induces an inhibitory signal through CD200R to Mφ.[90] Knowledge of the physiologic relevance of CD200-CD200R interaction in vivo came from studies of CD200^{-/-} animals. Naïve CD200^{-/-} animals constitutively show some degree of myeloid expansion and Mφ activation. However, CD200^{-/-} animals show much faster disease progression and significantly more susceptibility to several autoimmune diseases, such as collagen induced experimental allergic encephalomyelitis (EAE), which is a mouse model for the human disease, multiple sclerosis.[91]

Conclusion

In recent years our understanding has improved significantly about how innate PRRs recognise nonself, modified self and self molecules and how an appropriate inflammatory response is mounted against microbes. Our knowledge has grown, concerning how initial recognition by PRRs instructs the shape and nature of protective adaptive responses against microbes. However, knowledge is still sketchy about how discriminatory responses are induced against self and nonself molecules and how successful pathogens evade innate recognition and responses by PRRs. Future research should study the mechanistic differences between tolerance induction in innate and adaptive immunity. Why is autoimmunity predominantly associated with adaptive rather than innate immune responses? Does innate immunity instruct the regulatory functions of adaptive immunity? Recent advances in molecular and cellular biology make it possible to study new aspects of innate immunity and to understand the causes of many infectious and immune pathologies.

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