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Ligand recognition by antigen-presenting cell C-type lectin receptors

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It is now appreciated that the range of ligands interacting with C-type lectin type receptors on antigen presenting cells includes endogenous self-molecules as well as pathogens and pathogen-derived ligands. Interestingly, not all interactions between these receptors and pathogenic ligands have beneficial outcomes, and it appears that some pathogens have evolved immunoevasive or immunosuppressive activities through receptors such as DC-SIGN. In addition to this, recent data indicate that the well-characterised macrophage mannose receptor is not essential to host defence against fungal pathogens, as previously thought, but has an important role in regulating endogenous glycoprotein clearance. New studies have also demonstrated that different ligand binding and/or sensing receptors collaborate for full and effective immune responses.

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Abbreviations

APC	antigen-presenting cell
BDCA	blood DC antigen
CLR	C-type lectin receptor
CRD	carbohydrate recognition domain
DC	dendritic cell
FN-II	fibronectin type II
ICAM	intercellular adhesion molecule
ITAM	immunotyrosine activatory motif
MØ	macrophage
MHC-I	MHC class I
MHC-II	MHC class II
MR	mannose receptor
PRR	pattern recognition receptor
TLR	Toll-like receptor

Introduction

Antigen-presenting cells (APCs) of the innate immune system include macrophages (MØs), dendritic cells (DCs) and B cells. These cells capture and process foreign antigens for presentation to T cells enabling efficient host defence and immunological memory. B cells are well equipped to recognize and take up a wide variety of antigens due to the presence of somatically variable surface immunoglobulins. DCs and MØs, however, rely on germ-line encoded cell-surface receptors to distinguish between harmless self antigens and pathogen-derived antigens against which immune responses are desirable [1]. Over the past number of years our understanding of APC cell surface receptor biology has increased greatly. In addition to the well-characterised opsonic receptors for γ-immunoglobulins (FcγRs) [2] and the complement receptors, such as complement receptor 3 (CR3) [3,4], APCs of the myeloid lineage express an array of non-opsonic pattern recognition receptors (PRRs), which have evolved to recognize pathogen-associated molecular patterns (PAMPs) [5], including lipids, carbohydrates and proteins. In addition to this, APCs express receptors such as those of the immunoglobulin (Ig) superfamily [6–8], which mediate interactions with host cells to regulate immune responses.

One of the most intensely studied families of PRRs is the Toll-like receptor (TLR) family, members of which respond to a wide variety of pathogen-derived material. These interactions lead to APC maturation and migration to lymph nodes for subsequent presentation of antigen-derived peptides to T cells (for a comprehensive review, see [9]). Although the TLRs play a central role in alerting APCs to the presence of pathogenic material it is not clear whether they are capable of capturing and taking up antigens [10•], and this function appears to be met by other families of PRRs, most notably the C-type lectin receptors (CLRs) [11•] and the scavenger receptors [12].

In recent years a wealth of information has emerged demonstrating diverse roles for CLRs during primary immune responses. These receptors function not only in pathogen recognition through the recognition of PAMPs but also in the recognition of endogenous ligands to mediate cell–cell interactions during immune responses. CLRs also bind soluble self antigens, leading to immune tolerance and maintenance of endogenous glycoprotein homeostasis [13]. Furthermore, co-operation between TLRs and CLRs has been demonstrated and it seems that appropriate immune responses rely on the interaction of many different antigen sensing and sampling mechanisms [14].

Understanding the molecular mechanisms governing APC discrimination of self and non-self antigens should

facilitate a better understanding of aberrant immune phenomena such as autoimmunity and chronic inflammatory diseases as well as informing the design of vaccines and other immuno-modulatory drugs. In this article, we discuss recent advances in our understanding of CLR immunobiology and the contribution they make to interactions with both pathogenic and endogenous ligands. Data concerning molecular mechanisms of ligand discrimination by these receptors will also be discussed.

Characteristics of C-type lectin receptors

The term CLR defines carbohydrate-binding molecules that bind ligands in a Ca^{2+}-dependent manner (see Table 1). CLRs expressed by MØs and DCs are predominantly type II transmembrane receptors with a single carbohydrate recognition domain (CRD) such as DC-SIGN [15], the related murine receptor family termed SIGN-related (SIGNR)1-4 [16], dectin-2 [17], langerin [18] and BDCA-2 (blood DC antigen-2) [19]. In addition to this there are type I CLRs, such as mannose receptor (MR) and DEC-205, which have multiple lectin-like domains, although not all of these act as functional CRDs [20]. Dectin-1 is a type II CLR [21,22] with a single CRD but differs from receptors such as DC-SIGN as it does not contain a standard Ca^{2+}-dependent CRD and is more similar to the CLRs expressed by NK cells that bind MHC class I (MHC-I) and MHC-I-like counter-receptors [23] (Figure 1).

True Ca^{2+}-dependent CLRs fall into two broad categories, those recognizing mannose-type ligands and those recognizing galactose-type ligands, which can be defined at the molecular level by the presence of a distinctive triplet of amino acids within the CRD; EPN (in one-letter amino-acid code) for mannose-type receptors or QPD (in one-letter amino-acid code) for galactose-type receptors [24]. Additionally, receptors such as MR can recognize sulphated carbohydrates present on endogenous glycoproteins via a cysteine-rich domain independently of its CRD [25]. Dectin-1 binds β-1,3- and β-1,6-linked glucans, which are found in abundance in the cell walls of fungi, via a unique carbohydrate-binding mechanism that is not yet fully understood but has recently been shown to rely on a group of amino acids within a predicted β-sheet forming part of the CRD [26•].

Pathogenic and endogenous ligands for CLRs

Despite the existence of a wide range of CLRs with similar or overlapping ligand specificity, and the apparent ability of CLRs to bind both self and non-self ligands, each receptor appears to have distinct functions depending on where and when it is expressed, the degree of cell surface multimerisation and the context in which the ligand is recognized (i.e. in the presence or absence of an inflammatory signal through other receptors such as the TLRs).

The DC-SIGN family

DC-SIGN was originally characterised as a receptor interacting with intercellular adhesion molecule (ICAM)-3 [15], mediating DC–T-cell interactions. It was subsequently also shown to bind ICAM-2 on vascular endothelial cells, regulating DC migration [27]; both of these interactions occur through *N*-linked high mannose structures (typically consisting of between five

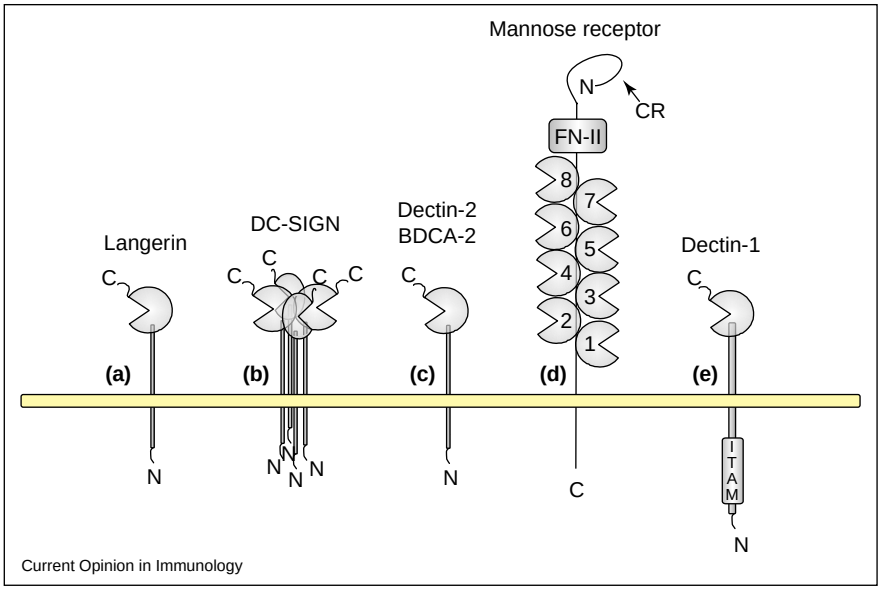
Table 1

C-type lectin receptors that bind endogenous and exogenous ligands.

Receptor	Type	Ligands (selected)	Expression	Regulation	References
MR	I	Endogenous and exogenous ligands bearing mannose, fucose, *N*-acetyl glucosamine and sulphated sugars via cysteine rich domain	MØ, DC subsets, lymphatic and hepatic endothelium	↑ PGE, IL-4, IL-10, IL-13 ↓ IFN-γ, LPS	[54,68,69]
Endo-180	I	Mannose, fucose and *N*- acetylglucosamine via CRD 2, collagen via FNII domain	Fibroblasts, MØ, subset of endothelial cells	Unknown	
DC-SIGN	II	HIV and other pathogens due to mannose type CRD. ICAM-2 and -3 via CRD.	DCs, alveolar and decidual MØ	↑ IL-13 ↓ LPS	[70]
DC-SIGNR	II	Similar to DC-SIGN	Hepatic and lymphatic endothelium	Unknown	
SIGNR1	II	Mannose-type CRD, dextran, *Streptococcus pneumoniae* CPS, *Candida albicans*, HIV, ICAM-3	MZ MØ, peritoneal MØ	Unknown	
Langerin	II	Mannose, fucose, *N*-acetylglucosamine	Langerhans cells, subset of DCs	↑ TGF-β↓ LPS, CD40-L	[71,72]
BDCA-2	II	Unknown	Plasmacytoid DCs	Unknown	
Dectin-2	II	Conflicting evidence for mannose type ligands $CD4^+/CD25^+$ T-cell ligand	DC, MØ, Langerhans cells	Unknown	
Dectin-1/β-glucan receptor	II	β-1,3- and β-1,6-linked glucans from fungi T-cell ligand	MØ, DC, PMN, T cell	↑ IL-4, IL-13 ↓ IL-10, LPS	[73]

Abbreviations: MZ, marginal zone; PGE, prostaglandin E.

Figure 1



The C-type lectin-like receptors expressed by dendritic cells and macrophages. These receptors permit interactions with pathogens and endogenous soluble proteins as well as cell-surface ligands expressed by T cells and anatomically distinct endothelial cells, such as those found in secondary lymphoid organs. Langerin **(a)**, a type-II C-type lectin expressed exclusively by Langerhans cells, binds mannose-type ligands and delivers material to unique Birbeck granules. DC-SIGN **(b)**, another type-II C-type lectin is expressed by both macrophages and DCs. It interacts with endogenous molecules, such as ICAM-2, on endothelial cells as well as ICAM-3 on T-cells, mediating intercellular adhesion. In addition, DC-SIGN binds pathogen-associated mannose-type carbohydrates found on viruses, bacteria and fungi. Multimerisation of DC-SIGN and other such receptors at the cell surface might facilitate high-affinity ligand binding. BDCA-2 **(c)**, is a C-type lectin expressed exclusively by human plasmacytoid DCs and appears to play a role in regulating type-I IFN production by these cells, although ligands for this receptor are yet to be identified. Dectin-2, a murine C-type lectin which demonstrates sequence similarity with BDCA-2 has a role in regulating UV-induced tolerance. This might be due to interaction with an as yet unidentified ligand on $CD4^+CD25^+$ T cells. Mannose receptor (MR) **(d)**, is a multi-functional type I receptor expressed by macrophages, DCs and endothelial cells. CRD 4 is the primary ligand-binding site for both endogenous and pathogen-derived mannosylated ligands. The CRD mediates interactions with sulphated carbohydrates found on endogenous ligands such as sialoadhesin and CD45. MR also mediates intercellular adhesion and can bind lymphocyte-expressed L-selectin. Dectin-1 **(e)**, is a non-classical C-type lectin found primarily on macrophages, DCs and neutrophils. It binds β-glucans in a Ca^{2+}-independent manner. Ligand-induced signalling mediated by the cytoplasmic ITAM motif leads to phagocytosis and pro-inflammatory cytokine production in co-operation with TLR-2.

and nine terminal mannose units). Mannose-dependent interactions also account for the ability of DC-SIGN to bind HIV [28] and a plethora of other pathogens, including *Mycobacterium tuberculosis*, *Candida albicans*, *Helicobacter pylori* and *Schistosoma mansoni* [29••]. DC-SIGN discriminates between ligands not only on the basis of primary mannose groups, but also via secondary binding sites, which accommodate carbohydrates with distinctive geometry conferred by linkage to the primary monosaccharide moiety [30••]. This probably explains the differences in ligand affinity between DC-SIGN and other apparent mannose-specific CLRs such as MR. Further specificity can also be achieved through multimerisation of the receptor at the cell surface [31]; indeed, tetramerisation of DC-SIGN facilitates high-affinity binding to high mannose oligosaccharides, such as those found on HIV [32•].

Despite the obvious ability of DC-SIGN to recognize pathogens, the contribution of this receptor to host defence is unclear. As ligands for DC-SIGN also bind many other CLRs, specific monoclonal antibodies have been used to assess the fate of ligands targeted through individual receptors [33]. Such studies indicate that DC-SIGN targets antigens to late endosomal/lysosomal compartments for degradation and presentation to T cells. Paradoxically, it has been reported that a range of viruses, including HIV [34], hepatitis C virus [35,36], the recently discovered coronavirus responsible for severe acute respiratory disease [37•], and dengue virus [38,39] can exploit DC-SIGN to protect virions from the normal pathways of lysosomal degradation and presentation to T cells. In the case of HIV, this interaction allows efficient transinfection of $CD4^+$ T cells in secondary lymphoid organs [34]. More recently, however, Moris and colleagues [40] have challenged this view by showing that, in DCs and DC-SIGN transfected cells, the majority of HIV virions are rapidly degraded in endosomal or lysosomal compartments. Although this pathway normally leads to MHC-II-restricted presentation of

epitopes, DC-SIGN-dependent MHC-I-restricted presentation was also evident. It is probable that not all virions are targeted in this way and a small proportion might escape to the cytoplasm or other non-endosomal/non-lysosomal compartments allowing subsequent transinfection of T cells. In addition, as DCs and MØs express many different mannose-specific CLRs, it is likely that virus uptake by these cells proceeds through multiple routes [41].

Data regarding the interaction of *M. tuberculosis* with DC-SIGN suggest that the pathogen has evolved to exploit the receptor as part of an immunoevasive strategy [42••]. Mannosylated lipoarabinomannan (ManLAM) is a mannose-capped glycolipid found in the cell wall of *M. tuberculosis*. It appears that ManLAM can induce the secretion of the immunosuppressive cytokine IL-10 from DCs in a DC-SIGN-dependent manner. This interaction also appears to inhibit the expression of co-stimulatory molecules required for efficient stimulation of adaptive immune responses that are normally induced by pathogenic ligands following TLR stimulation.

SIGNR1, one of five murine homologues of the DC-SIGN family of receptors, is essential for the clearance of *Streptococcus pneumoniae*-derived capsular polysaccharides by marginal zone MØs [43]. Although the fate of antigens cleared in this way is not yet known, a study by the same group [44] indicates that dextran is targeted to non-lysosomal compartments in a SIGNR1-transfected MØ cell line. SIGNR1 is also a non-opsonic receptor for yeasts such as *Candida albicans* [45]. Although it cannot efficiently internalise antigen by itself, it might play an important role in trapping ligands at the cell surface, thereby facilitating recognition and uptake by other PRRs such as dectin-1.

The mannose receptor family

The MR family of multi-lectin receptors includes MR itself as well as Endo-180, DEC-205 and the phospholipase A_2 receptor [20]. Of these, only MR and Endo-180 have the capacity to bind carbohydrates in a Ca^{2+}-dependent manner via their CRDs.

MR is the best characterised of these receptors and binds a range of bacteria, yeasts and viruses through interactions between a mannose-type CRD and pathogen-associated high mannose structures. The ability of MR to enhance uptake and processing of mannosylated antigens for presentation by MHC-II [46] has recently been challenged by studies using transfected fibroblasts [47]. MR does, however, appear to have a specialized role in the delivery of pathogen-associated glycolipids, such as lipoarabinomannan, for presentation on CD1b [48].

Although the mannose-type CRD of Endo-180 has a similar ligand spectrum as MR [49], its role as a pathogen clearance receptor has not been investigated. Endo-180 is best known as a fibroblast-expressed receptor for collagen [50], which binds collagen via an amino-terminal fibronectin type II (FN-II) domain, and Endo-180-deficient mice have defects in collagen uptake [51••]. The MR itself also contains a FN-II domain although there are currently no published data regarding its ability to bind collagen. By contrast, the cysteine rich domain of MR endows a capacity to bind endogenous glycoproteins such as sialoadhesin and CD45 bearing sulphated *N*-acetyl galactosamine or galactose moieties [25], which are expressed by metallophillic MØs in secondary lymphoid organs [52,53]. These cells are located adjacent to B-cell follicles, and such interactions might influence immune responses to ligands targeted to these cells that might be delivered by a naturally occurring soluble form of the receptor [54,55]. In addition to these ligands, MR also mediates the clearance of potentially harmful endogenous inflammatory glycoproteins bearing ligands for the mannose-type CRD [56,57].

The relative importance of MR interactions with such a diverse array of ligands has recently been clarified following the generation of MR-deficient mice by two separate groups [58,59]. Surprisingly, MR does not appear to be essential for primary immune responses against fungal pathogens, and $MR^{-/-}$ mice are no more susceptible to infection by these pathogens than their wild-type counterparts when mortality and disseminated infection are measured [60••,61••]. By contrast, these mice have increased plasma concentrations of endogenous glycoproteins, such as lysosomal hydrolases, confirming an important role for MR in the clearance of self antigens. MR also plays an important role in fertility by controlling levels of the glycosylated pituitary hormone, lutropin. $MR^{+/-}$ mice have decreased litter sizes as a result of abnormalities in the pulsatile release of this hormone [59].

Dectin-1: a pattern-recognition receptor for fungal pathogens

The absence of immune defects in $MR^{-/-}$ mice in response to fungal pathogens highlights the presence of other PRRs responsible for dealing with these microbes. The identification of dectin-1 as a CLR that mediates innate immune responses to β-1,3- and β-1,6-linked glucans present in fungal cell walls [22] is a major advance in our understanding of host responses to such pathogens.

Although many of the other CLRs described in this article participate in the clearance of glycosylated antigens, dectin-1 is unusual as it also plays a central role in eliciting pro-inflammatory mediators such as TNF-α in response to fungal pathogens [62••]. The majority of pro-inflammatory responses to pathogenic ligands are mediated by the TLR family of PRRs and, in the case of dectin-1, collaboration with TLR2 is essential to the response

[62••,63••]. Dectin-1 contains an immunotyrosine activatory motif (ITAM) within its cytoplasmic tail that is required for interactions with the TLR2 signalling pathway. Independently of TLR2, the ITAM is also required for cytoskeletal rearrangements triggered through dectin-1 preceding phagocytosis [64]. The precise signalling pathways initiated following tyrosine phosphorylation within the ITAM are not well understood. Although it was initially predicted that they might be similar to those seen with other ITAM-bearing receptors, such as the Fc receptors for IgG, a new study suggests that this is not the case and it is likely that dectin-1 responses act through a novel signalling pathway [64].

Interestingly, the intracellular fate of ligands captured through dectin-1 appears to be associated with their size [64]. Receptors such as MR rapidly recycle between the cell surface and lysosomal vesicles where ligands are released and degraded allowing MR to traffic back to the cell surface [20]. Other receptors such as FcγR undergo *de novo* synthesis and are degraded in lysosomes together with their cargo [65]. Dectin-1, however, has features of both types of trafficking depending on the ligand used. When stimulated with smaller ligands such as laminarin, the receptor recycles to the cell surface but when larger ligands such as glucan phosphate or zymosan are used cell surface dectin-1 expression is reduced [20]. The mechanism of this trafficking is unclear at present but might have significant implications for our understanding of the biological effects of dectin-1 ligands *in vivo* as well as our understanding of antigen handling by the innate immune system.

As with other CLRs discussed in this review, dectin-1 also interacts with an endogenous ligand present on activated T cells and this can lead to T-cell proliferation when a second stimulus is delivered through CD3 [21]. A more recent study using a short isoform of dectin-1 indicates that it can stimulate both $CD4^+$ and $CD8^+$ T cells, inducing co-stimulatory molecule expression and IFN-γ production [66]. Although the nature of this T-cell ligand is unknown, it is known that the interaction occurs through a distinct site from that mediating β-glucan recognition [67].

Conclusions

In recent years our understanding of CLRs has expanded greatly. Beyond their roles as PRRs recognizing pathogens and pathogen-derived ligands, these receptors also interact with a wide range of known and unknown endogenous ligands. Further characterisation of these interactions will be vital to a full understanding of CLR biology. The absence of primary immune defects in $MR^{-/-}$ mice is surprising and it probably reflects an historical attribution of mannose inhibitable phenomena in the literature to MR before the discovery of other APC-expressed mannose-type CLRs.

The generation of knockout models for these other CLRs should allow us to clarify the individual functions of these receptors in immune and non-immune phenomena. The coming years should further expand our knowledge of the roles played by CLRs in the immune system. Two major issues will be: the identification and characterisation of endogenous ligands observed for CLRs such as dectin-1 and dectin-2; and, understanding the full signalling capacity of CLRs and their interaction with other antigen sensing receptors.

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