Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Levels of complexity in pathogen recognition by C-type lectins

Alessandra Cambi and Carl G Figdor

In pathogen recognition by C-type lectins, several levels of complexity can be distinguished; these might modulate the immune response in different ways. Firstly, the pathogen-associated molecular pattern repertoire expressed at the microbial surface determines the interactions with specific receptors. Secondly, each immune cell type possesses a specific set of pathogen-recognition receptors. Thirdly, changes in the cell-surface distribution of C-type lectins regulate carbohydrate binding by modulating receptor affinity for different ligands. Crosstalk between these receptors results in a network of multimolecular complexes, adding a further level of complexity in pathogen recognition.

Addresses
Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Corresponding author: Figdor, Carl G (c.figdor@ncmls.ru.nl)

Introduction
C-type lectin receptors (CLRs) are proteins that contain carbohydrate recognition domains (CRDs) and bind carbohydrate structures in a Ca\(^{2+}\)-dependent manner. Ca\(^{2+}\) ions are directly involved in ligand binding, as well as in maintaining the structural integrity of the CRD that is necessary for the lectin activity [1]. Depending on the amino acid sequence, the CRD has specificity for mannose, galactose or fucose structures. Moreover, interaction of these carbohydrate structures with the different CLRs is dependent on carbohydrate branching, spacing and multivalency.

CLRs are either produced as transmembrane proteins or are secreted as soluble proteins (Table 1). They have been shown to act both as adhesion and as pathogen-recognition receptors [2]. The broad selectivity of the monosaccharide-binding site and the geometrical arrangement of multiple CRDs provide a first basis for discriminating between self and non-self [3]. Thus, CLRs recognize carbohydrate patterns expressed by the invading microorganisms and have a role in both innate and adaptive immunity [4]. Several microorganisms have developed strategies for exploiting the CLR-mediated uptake to their benefit, and evade the host immune defenses [5,6].

In this review, we focus on the role of CLRs in the recognition of pathogens that leads either to immune protection or immune evasion. We discuss binding specificity as a consequence of differences in ligand glycosylation, the molecular and structural elements that regulate the interaction with pathogen-associated molecular patterns (PAMPs) and, finally, the increasing evidence of interactions with other immune receptor families, which adds to the complexity of CLR-mediated pathogen recognition.

Identification of new carbohydrate structures
Recent findings reported by several investigators indicate that CLRs recognize subtle differences in the arrangement and branching of the carbohydrate residues. Despite the fact that several CLRs share a CRD and bind mannose-containing structures, different branching and spacing of these structures create unique sets of carbohydrate-recognition profiles for each receptor.

Therapeutic manipulation of carbohydrate–protein interactions requires detailed knowledge of the specific spectrum of carbohydrate structures recognized by each CLR. Oligosaccharide microarray technologies are currently being applied to facilitate a systematic and high-throughput analysis of protein–carbohydrate interactions.

A well-known example is the neoglycolipid technology that generates lipid-linked oligosaccharide arrays from glycoproteins, glycolipids, proteoglycans, polysaccharides, whole organs or chemically synthesized oligosaccharides [7]. By glycan array profiling, discrimination between high- and low-affinity carbohydrate ligands for the murine CLRs specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin (SIGN)-R1, SIGN-R3 and langerin has been achieved [8].

Alternative glycan arrays have also been documented. Recently, Guo et al. [9] showed that dendritic cell (DC)-SIGN and its homolog L-SIGN have distinct ligand-binding properties. Whereas L-SIGN was only able to bind to mannose-containing ligands, DC-SIGN reacted with many more glycans, including fucose moieties on Lewis blood group antigens [9]. The observation that DC-SIGN and L-SIGN differ in their
Several new carbohydrate structures have been identified as key components of the innate immunity in lung alveoli, particularly for other CLRs, such as surfactant protein (SP)-D and L-SIGN [12]. This is important for ICAM-2 and ICAM-3 interactions with DC-SIGN [11]. The mannosylated lipoarabinomannan of Mycobacterium tuberculosis serves as a ligand for DC-SIGN and its homologs L-SIGN and murine SIGN-R1 [10].

The specific carbohydrate structure recognized by DC-SIGN and its homologs L-SIGN and murine SIGN-R1 on mycobacterial mannosylated lipoarabinomannan was also identified, all receptors showing similar affinity for the mannose-cap oligosaccharide (man)3-ara (Table 1) [11].

Finally, biochemical studies using mutants of DC-SIGN demonstrated that binding to the HIV envelope protein gp120 is mediated by a distinct but overlapping epitope when compared with ICAM-2 and ICAM-3, providing a rationale for specific targeting of the gp120–DC-SIGN interaction, without affecting other physiologically important ICAM-2 and ICAM-3 interactions with DC-SIGN [12].

Several new carbohydrate structures have been identified for other CLRs, such as surfactant protein (SP)-D (Table 1). Despite the fact that this soluble CLR is a key component of the innate immunity in lung alveoli, limited information is available on its binding to complex carbohydrate structures. Recently, by using surface plasmon resonance spectroscopy, van de Wetering et al. [13] identified terminal α-1-3-linked fucose residues as strong ligands for SP-D. Furthermore, for the first time, SP-D was shown to bind multicellular larval stages of the parasitic worm Schistosoma mansoni, transiently residing in the lung, by interacting with these fucosylated glycans exposed at the cell surface [13].

Novel binding targets were also identified in the interaction between the collectin mannose-binding lectin (MBL) and the bacterium Neisseria meningitidis (Table 1). Surprisingly, MBL was found to bind meningococci via two nonglycosylated major outer membrane proteins, opacity protein and porin, of N. meningitidis [14]. Binding of CLR to nonsugar targets on the surface of pathogens might further increase the complexity of pathogen–CLR interactions.

### C-type lectin oligomerization: multivalent microdomains bind to microbial surfaces

The capacity of CLRs to detect microorganisms depends on the density of the PAMP present on the microbial surface, as well as on the degree of oligomerization of the lectin receptor. In fact, the assembly of several CRDs in multimers points the binding sites towards a common direction, increasing the binding valency and allowing interactions with the dense carbohydrate arrays on microbial surfaces.

#### Table 1

| Group       | Molecular structure   | C-type lectin      | Newly identified pathogens [specific ligand]                                                                 | References |
|-------------|-----------------------|--------------------|--------------------------------------------------------------------------------------------------------------|------------|
| Collectins  | Soluble               | MBL                | Neisseria meningitidis [nonglycosylated outer membrane opacity protein and porin]                           | [14]       |
|             |                       | SP-A               | Mycobacterium avium [lipoarabinomannan]                                                                    | [38]       |
|             |                       | SP-D               | Mycobacterium avium [lipoarabinomannan]                                                                    | [38]       |
|             |                       |                    | Schistosoma mansoni [α-1-3-linked fucose]                                                                  | [13]       |
|             |                       |                    | All three members (MBL, SP-A and SP-D) bind free DNA and apoptotic cell-derived DNA                          | [42]       |
| Type II receptors | Type II transmembrane | DC-SIGN            | Hepatitis C virus [E1 and E2 glycoproteins]                                                              | [43]       |
|             |                       |                    | Marburg virus [GP-glycoprotein]                                                                           | [44]       |
|             |                       |                    | SARS-CoV [S-glycoprotein]                                                                                  | [44]       |
|             |                       |                    | Helicobacter pylori [Lewis X/Y LPS]                                                                         | [26]       |
|             |                       |                    | Aspergillus fumigatus [galactomannan]                                                                     | [45]       |
|             |                       |                    | Mycobacterium tuberculosis [(man)3-ara]                                                                    | [11]       |
| Type I receptors | Type I transmembrane | L-SIGN             | Hepatitis C virus [E1 and E2 glycoproteins]                                                              | [43]       |
|             |                       |                    | Marburg virus [GP-glycoprotein]                                                                           | [44]       |
|             |                       |                    | SARS-CoV [S-glycoprotein]                                                                                  | [44, 46]   |
|             |                       |                    | Mycobacterium tuberculosis [(man)3-ara]                                                                    | [11]       |
|             |                       |                    | Schistosoma mansoni                                                                                        | [10]       |
|             |                       | mSIGN-R1           | Streptococcus pneumoniae [capsular polysaccharide]                                                        | [47]       |
|             |                       |                    | Mycobacterium tuberculosis [(man)3-ara]                                                                    | [11]       |
|             |                       | Langerin           | Mycobacterium leprae [nonpeptide antigen]                                                                  | [33]       |

* Group is determined by nomenclature in use at ‘A genomics resource for animal lectins’ (URL: http://ctld.glycob.ox.ac.uk).

b SARS-CoV, severe acute respiratory syndrome coronavirus. Note that this table is limited to novel ligands identified in 2004; a more extensive description is given in [48].
The collectins form trimers, which further assemble into larger oligomers, appearing as a ‘bouquet of flowers’ [15]. Mutations that hamper the assembly of human MBL into oligomers result in a reduced capability to activate components of the complement system, thus increasing both the risk and severity of infections and leading to autoimmunity [16].

Moreover, transmembrane CLRs have developed several strategies to increase their strength of binding to PAMPs. Proteomic analysis of membrane-purified DC-SIGN complexes showed that DC-SIGN exists as tetramers at the surface of immature monocyte-derived DCs, and that this assembly is required for high-affinity binding of glycoproteins such as HIV gp120 [17]. Moreover, biochemical and hydrodynamic studies on truncated DC-SIGN demonstrated that the portion of the neck of each molecule adjacent to the CRD is sufficient to mediate the formation of dimers, whereas the neck regions near the amino-terminal are required to stabilize tetramers [18]. In the same study, it was also shown that the CRDs are flexibly linked to the neck regions, which project CRDs from the cell surface and enable DC-SIGN to bind to various glycans on microbial surfaces [18].

Recently, we observed that DC-SIGN showed higher levels of organization (clustering) on the surface of DCs, depending upon the differentiation state of the DCs when they developed from monocytic precursors [19]. High-resolution electron microscopy images demonstrated a direct relationship between DC-SIGN function as a viral receptor and its microlocalization on the plasma membrane. During development of human monocyte-derived DCs, DC-SIGN organization changes from a random distribution pattern into well-defined microdomains on the cell membrane. These submicron-sized microdomains have an average diameter of 100–200 nm, as established by electron microscopy and near-field scanning optical microscopy [20]. The organization of DC-SIGN in microdomains on the plasma membrane is important for the binding and internalization of virus particles, suggesting that these multimolecular assemblies of DC-SIGN act as a docking site for pathogens such as HIV-1 to invade the host [19].

Further investigation is necessary to establish whether also other CLRs are organized in similar multi-molecular assemblies at the cell membrane.

**Pathogen recognition by C-type lectins: protection or evasion?**

There is increasing evidence to suggest that pathogens use several strategies to evade host immune surveillance [5,6].

DC-SIGN was first identified as an HIV-1 receptor that enhanced infection of T lymphocytes in trans [21]. Recently, Arrighi et al. [22] demonstrated that DC-SIGN is required for the formation of an infectious synapse between HIV-1-bearing DCs and resting CD4+ T cells. More specifically, the use of small RNAi-expressing lentiviral vectors specifically to knock down DC-SIGN on DCs showed that DC-SIGN-DCs are still able to internalize HIV-1, although the binding of virions was found to be reduced, but they cannot transfer HIV-1 infection to target cells [22]. It is becoming clear that other viruses besides HIV-1 target DC-SIGN to promote their dissemination and modulate DC function for establishing chronic infections. Hepatitis C virus has recently been shown to target DC-SIGN and L-SIGN to escape lysosomal degradation [24]. Similarly, severe acute respiratory syndrome coronavirus binds to DC-SIGN and is transferred by DCs to susceptible target cells through a synapse-like structure [25].

In addition to viruses, Helicobacter pylori has also been demonstrated to target DC-SIGN to block a polarized Th1 response [26]. This bacterium binds to DC-SIGN via its lipopolysaccharide (LPS), which exposes Lewis blood group antigens. In particular, reversible on-off switching of specific fusosyltransferases regulates the expression of Lewis-X and -Y on the LPS, thus causing LPS phase variation (Lewis-X’/Y’ and Lewis-X/Y) within a strain. Interestingly, whereas Lewis-X’/Y’ H. pylori escapes binding to DCs, the Lewis-X/Y’ phase variant exploits binding to DC-SIGN to increase interleukin-10 levels and block the skewing of naïve T cells to Th1 cells [26].

A similar evasion strategy has also been developed by the yeast-like fungus Cryptococcus neoformans, which infects the respiratory and nervous systems, to escape aggregation by SP-D [27]. Only acapsular C. neoformans is aggregated by SP-D and subsequently removed by microciliary clearance. Therefore, after deposition in the lung, C. neoformans readily starts producing a capsule, thus also releasing soluble capsular components, including glucuronoxylomannan (GXM). SP-D binds with high affinity to soluble glucuronoxylomannan, and this interaction has been shown to inhibit SP-D aggregation of acapsular C. neoformans, thus interfering with pathogen clearance [27].

Bordetella pertussis, the causative agent of human whooping cough, uses a slightly different mechanism for resisting the bactericidal effects of SP-A [28]. SP-A binds via its CRD to the lipid A component of LPS. However, B. pertussis LPS has a terminal trisaccharide which apparently shields the bacteria from SP-A-mediated clearance by sterically limiting access of SP-A to the lipid A region [28].

Despite these examples of immune evasion by pathogens through CLRs, we must not forget that these receptors...
have a fundamental role in limiting the early proliferation of infectious microorganisms. The importance of MBL in restricting the complications associated with *Staphylococcus aureus* infection is highlighted by studies involving MBL-null mice [29]. This *in vivo* study demonstrated that 100% of the MBL-null mice died 48 hours after exposure to an intravenous inoculation of *S. aureus* compared with a 45% mortality rate in wild-type mice [29]. Similarly, SP-D knockout mice displayed a delayed clearance of *Pneumocystis carinii* infection, increased inflammation and altered nitric oxide metabolism [30].

Interestingly, although DC-SIGN is exploited by several viruses to escape lysosomal degradation, Moris *et al.* [31] recently demonstrated that DC-SIGN does not always protect captured virions against degradation. In fact, a fraction of the incoming viral material is processed by the proteasome and leads to activation of anti-HIV-specific cytotoxic T lymphocytes by DC-SIGN-expressing cells [31]. This work suggests that the different routing of the incoming viral material might be directly related to the viral load. Additional evidence for a protective *in vivo* role for a SIGN family member is provided by Lanoue *et al.* [32]. Mice lacking SIGN-R1 are significantly more susceptible to *Streptococcus pneumoniae* infection and fail to clear the bacteria from the circulation, showing an important role for SIGN-R1 in the protection against sepsis [32*].

The Langerhans cell-specific C-type lectin langerin has also been shown to have a crucial role in the generation of CD1a-restricted T cell clones against a *Mycobacterium leprae* lipid antigen [33*].

Recent findings have demonstrated that Pneumocystis induces nuclear translocation of nuclear factor-κB in human alveolar macrophages primarily through interactions with the macrophage mannose receptor (MMR) [34]. This identifies the MMR as a pattern recognition receptor (PRR) which, besides mediating phagocytosis, is also capable of signaling in response to infectious non-self challenge.

Levels of complexity in pathogen recognition

In the past few years, evidence has accumulated illustrating the important role of the C-type lectins for the normal functioning of the immune system. From this, a picture is emerging that suggests that microbial recognition is based on networks between C-type lectins and other innate immune recognition receptors.

For example, the lectin pathway of complement activation is essential in innate antimicrobial defense. This is initiated by multimolecular complexes composed of MBL and MBL-associated serine proteases, which subsequently cleave complement C4 and C2, thus triggering the complement cascade. Studies with both MBL-null mice and MBL-deficient individuals have demonstrated that the absence of MBL-mediated complement activation severely increases susceptibility to herpes simplex virus-2 infection [35]. Similarly, a direct interaction of MBL with *Candida albicans* has been documented; this was shown to result in agglutination and accelerated complement activation and to lead to fungal growth inhibition, even in the absence of opsonophagocytosis by DCs [36].

Interestingly, cooperation among members of the C-type lectin family has also been reported. Taylor *et al.* [37] demonstrated that in murine peritoneal macrophages, SIGN-R1 exhibits additive cooperation with the β-glucan receptor dectin-1 in the nonopsonic recognition of yeast.

In addition, SP-A and SP-D, but not MBL, have been shown to enhance phagocytosis of *Mycobacterium avium* by macrophages through upregulation of MMR cell-surface expression and activity [38].

Furthermore, SP-A has been reported to augment the phagocytosis of *S. pneumoniae* by alveolar macrophages through an increase in cell-surface localization of scavenger receptor A [39].

These recent observations, together with previous reports documenting crosstalk between C-type lectins and TLRs [40,41], clearly indicate that specific interactions among different immune receptors might differentially regulate the outcome of an immune response against a specific pathogen.

Conclusions

In the recognition of pathogens, several levels of complexity can be distinguished that might determine the destiny of the pathogen and the outcome of an immune response (Figure 1). Firstly, the pathogen itself expresses at its surface a specific PAMP, or a combination of different PAMPs, which dictates the recognition by specific receptors. Secondly, the set of PRRs expressed varies among different cells, resulting in a specific set of pathogen-recognition receptors which is different for each cell type of the immune system. Thirdly, changes in PRR cell-surface distribution adds yet another level of complexity, modulating the binding to certain carbohydrate moieties, and thus regulating the affinity for different ligands. Finally, these receptors have been shown to interact with each other, thereby giving rise to a network of multimolecular complexes that add a fourth level of complexity to pathogen recognition. Unraveling the precise mechanisms regulating the formation and exact function of these receptor networks is the present challenge.
Pathogen recognition by C-type lectins

Cambi and Figdor

Levels of complexity in lectin-mediated pathogen recognition determine pathogen destiny and the immune response. Differences in PAMPS expressed by pathogens and PRRs on host cells determine a first and second level of complexity in recognition. (a) Changes in receptor distribution at the cell surface might further influence the binding to a pathogen and the subsequent intracellular routing of the pathogen, and determine pathogen survival or lysosomal degradation. (b) The formation of mixed multimolecular receptor assemblies (for example, between CLRs and TLRs, complement receptors or other CLRs) might further extend the PAMP profile. Moreover, the outcome of a cell response to a pathogen (for example, in terms of the release of different cytokines) might differ depending on the triggering of single receptors or receptor complexes.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

● of special interest

●● of outstanding interest

1. Drickamer K: C-type lectin-like domains. Curr Opin Struct Biol 1999, 9:585-590.

2. Cambi A, Figdor CG: Dual function of C-type lectin-like receptors in the immune system. Curr Opin Cell Biol 2003, 15:539-546.

3. Geijtenbeek TB, van Vliet SJ, Engering A, 't Hart BA, van Kooyk Y: Self- and nonself-recognition by C-type lectins on dendritic cells. Annu Rev Immunol 2004, 22:33-54.

4. Figdor CG, van Kooyk Y, Adema GJ: C-type lectin receptors on dendritic cells and Langerhans cells. Nat Rev Immunol 2002, 2:77-84.

5. van Kooyk Y, Geijtenbeek TB: DC-SIGN: escape mechanism for pathogens. Nat Rev Immunol 2003, 3:697-709.

6. van Kooyk Y, Engering A, Lekkerkerker AN, Ludwig IS, Geijtenbeek TB: Pathogens use carbohydrates to escape immunity induced by dendritic cells. Curr Opin Immunol 2004, 16:488-493.

7. Feizi T, Chai W: Oligosaccharide microarrays to decipher the glyco code. Nat Rev Mol Cell Biol 2004, 5:582-588.

8. Galustian C, Park CG, Chai W, Kiso M, Bruening SA, Kang YS, Steinman RM, Feizi T: High and low affinity carbohydrate ligands revealed for murine SIGN-R1 by carbohydrate array and cell binding approaches, and differing specificities for SIGN-R3 and langerin. Int Immunol 2004, 16:853-866.

Both this study and that described in reference 9 highlight the importance of a detailed knowledge of the carbohydrate-binding profile and discuss two high-throughput methods that allow the identification of novel carbohydrate structures recognized by receptors.

9. Guo Y, Feinberg H, Conroy E, Mitchell DA, Alvarez R, Blixt O, Taylor ME, Weis WI, Drickamer K: Structural basis for distinct ligand-binding and targeting properties of the receptors DC-SIGN and DC-SIGNR. Nat Struct Mol Biol 2004, 11:591-598.

See annotation to [8].

10. Van Liempt E, Imberty A, Bank CM, Van Vliet SJ, Van Kooyk Y, Geijtenbeek TB, Van Die I: Molecular basis of the differences in binding properties of the highly related C-type lectins DC-SIGN and L-SIGN to Lewis X trisaccharide and Schistosoma mansoni egg antigens. J Biol Chem 2004, 279:33161-33167.

This study shows for the first time a clear correlation between specific carbohydrate recognition and amino acid sequence, and clearly explains the different carbohydrate-binding profiles of the two homologs DC-SIGN and L-SIGN.

11. Koppel EA, Ludwig IS, Hernandez MS, Lowary TL, Gadikota RR, Tuzikov AB, Vandenbroucke-Grauls CM, van Kooyk Y, Appelmelk BJ, Geijtenbeek TB: Identification of the mycobacterial carbohydrate structure that binds the C-type lectins DC-SIGN, L-SIGN and SIGNR1. Immunobiology 2004, 209:117-127.
Host-pathogen interactions

12. Su SV, Hong P, Baik S, Negrete OA, Gurney KB, Lee B: DC-SIGN binds to HIV-1 glycoprotein 120 in a distinct but overlapping fashion compared with ICAM-2 and ICAM-3. J Biol Chem 2004, 279:19122-19132.

13. van de Wetering JK, van Remoortere A, Vaandrager AB, Collectins and

15. Lu J, Teh C, Kishore U, Reid KB: Both this study and that described in reference 33 indicate the existence of an interaction between C-type lectins and nonsugar moieties.

16. Larsen F, Madsen HO, Sim RB, Koch C, Garred P: Disease-associated mutations in human mannose-binding lectin compromise oligomerization and activity of the final protein. J Biol Chem 2004, 279:21302-21311.

17. Bernhard OK, Lai J, Wilkinson J, Shell MM, Cunningham AL: Protoemetic analysis of DC-SIGN on dendritic cells detects tetramers required for ligand binding but no association with CD4. J Biol Chem 2004, 279:51828-51835.

19. Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van der Wetering JK, van Remoortere A, Vaandrager AB, Collectins and

21. Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Hulst NF, Garcia-Parajo MF: This study provides a clear demonstration that tetramerization of DC-SIGN does occur at the cell membrane.

22. Koopman M, Cambi A, de Bakker BI, Joosten B, Figdor CG, de Lange F, van Maarseveen NM, Nijhuis M, Joosten B, et al.: DC-SIGN-mediated infectious transduction of the receptors DC-SIGN and DC-SIGNR. J Biol Chem 2005, 280:1327-1335.

28. Schaeffer LM, McCormack FX, Wu H, Weiss AA: Bordetella pertussis lipopolysaccharide resists the bactericidal effects of pulmonary surfactant protein A. J Immunol 2004, 173:1959-1965.

31. Kuronuma K, Sano H, Kato K, Kudo K, Hyakushima N, Yokota S, Abraham S, Leuba F, Dutoit V, Ducrey-Rundquist O, van Kooyk Y et al.: Lentivirus-mediated RNA interference of DC-SIGN contributes to protection against lethal pneumococcal infection in mice. J Exp Med 2004, 200:1383-1393.

34. Zhang J, Zhu J, Imrich A, Cushion M, Kinane TB, Koziel H: See annotation to [37]

35. Gadjeva M, Paludan SR, Thiel S, Slavov V, Ruseva M, Brennan PJ, Belisle JT, Blauvelt A, Porcelli SA et al.: Langerhans cells utilize CD1a and langerin to efficiently present nonpeptide antigens to T cells. J Clin Invest 2004, 113:701-708. See annotation to [14].

37. Kudo K, Takahashi K, Dundeet J, Shahroor-Karni S, Thiel S, Jensenius JC, Gad F, Hamblin MR, Sastry KN, Ezekowitz RA: Mannose-binding lectin-deficient mice are susceptible to infection with Staphylococcus aureus. J Exp Med 2004, 200:1379-1390.

39. Kuronuma K, Sano H, Kato K, Kudo K, Hyakushima N, Yokota S, Abraham S, Leuba F, Dutoit V, Ducrey-Rundquist O, van Kooyk Y et al.: Mannose-binding lectin-deficient mice are susceptible to infection with Staphylococcus aureus. J Exp Med 2004, 200:1379-1390.

42. Arrihi JF, Pion M, Garcia E, Escola JM, van Kooiyh Y, Geijtenbeek TB, Piguet V: DC-SIGN-mediated infectious synapse formation enhances X4 HIV-1 transmission from dendritic cells to T cells. J Exp Med 2004, 200:1279-1288.

43. Arrihi JF, Pion M, Wiznerowicz M, Geijtenbeek TB, Garcia E, Abraham S, Leuba F, Dutot V, Ducrey-Rundquist O, van Kooiyh Y et al.: Lentivirus-mediated RNA interference of DC-SIGN expression inhibits human immunodeficiency virus transmission from dendritic cells to T cells. J Virol 2004, 78:10848-10855.

46. Ludwig IS, Lekkerkerker AN, Depla E, Bosman F, Musters RJ, Depaertere S, van Kooiyh Y, Geijtenbeek TB: Hepatitis C virus targets DC-SIGN and L-Escape to losssomal degradation. J Virol 2004, 78:8322-8332.

48. Kudo K, Sano H, Kato K, Kudo K, Hyakushima N, Yokota S, Takahashi K, Fuji S, Fujii N, Shimada K, Yano I, Kumazawa Y, Voelker DR et al.: Pulmonary surfactant protein A enhances phagocytosis of Mycobacterium avium through increased activity of mannose receptor. J Immunol 2004, 172:7592-7602. See annotation to [37].

50. Taylor PR, Brown GD, Herre J, Williams DL, Willment JA. Gordon S: The role of SIGNR1 and the beta-glucan receptor (dectin-1) in the nonopsonic recognition of yeast by specific macrophages. J Immunol 2004, 172:1157-1162.

53. Kudo K, Sano H, Kato K, Kudo K, Hyakushima N, Yokota S, Takahashi K, Fuji S, Suzuki H, Kodama T et al.: Pulmonary surfactant protein A enhances phagocytosis of Streptococcus pneumoniae by alveolar macrophages through a casein kinase 2-dependent increase of cell surface localization of scavenger receptor A. J Biol Chem 2004, 279:21421-21430.
40. Brown GD, Herre J, Williams DL, Willment JA, Marshall AS, Gordon S: Dectin-1 mediates the biological effects of beta-glucans. J Exp Med 2003, 197:1119-1124.

41. Geijtenbeek TB, Van Vliet SJ, Koppel EA, Sanchez-Hernandez M, Vandenbroucke-Grauls CM, Appelmelk B, Van Kooyk Y: Mycobacteria target DC-SIGN to suppress dendritic cell function. J Exp Med 2003, 197:7-17.

42. Palaniyar N, Nadesalingam J, Clark H, Shih MJ, Dodds AW, Reid KB: Nucleic acid is a novel ligand for innate, immune pattern recognition collects surfactant proteins A and D and mannose-binding lectin. J Biol Chem 2004, 279:32728-32736.

This study identifies nucleic acids as novel ligand structures for C-type lectins and indicates a possible role for these receptors in the clearance of apoptotic cells.

43. Cormier EG, Durso RJ, Tsamis F, Boussemart L, Manix C, Olson WC, Gardner JP, Dragic T: L-SIGN (CD209L) and DC-SIGN (CD209) mediate transinfection of liver cells by hepatitis C virus. Proc Natl Acad Sci USA 2004, 101:14067-14072.

44. Marzi A, Gramberg T, Simmons G, Moller P, Rennekamp AJ, Krumbiegel M, Geier M, Eisemann J, Turza N, Saunier B et al.: DC-SIGN and DC-SIGNR interact with the glycoprotein of Marburg virus and the S protein of severe acute respiratory syndrome coronavirus. J Virol 2004, 78:12090-12095.

45. Serrano-Gomez D, Dominguez-Soto A, Ancochea J, Jimenez-Heffernan JA, Leal JA, Corbi AL: Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin mediates binding and internalization of Aspergillus fumigatus conidia by dendritic cells and macrophages. J Immunol 2004, 173:5635-5643.

46. Jeffers SA, Tusell SM, Gillim-Ross L, Hemmila EM, Achenbach JE, Babcock GJ, Thomas WD Jr, Thackray LB, Young MD, Mason RJ et al.: CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. Proc Natl Acad Sci USA 2004, 101:15748-15753.

47. Kang YS, Kim JY, Bruening SA, Pack M, Charalambous A, Pritsker A, Moran TM, Loefler JM, Steinman RM, Park CG: The C-type lectin SIGN-R1 mediates uptake of the capsular polysaccharide of Streptococcus pneumoniae in the marginal zone of mouse spleen. Proc Natl Acad Sci USA 2004, 101:215-220.

48. Cambi A, Koopman M, Figdor CG: How C-type lectins detect pathogens. Cell Microbiol 2005, 7:481-488.