Microreview

How C-type lectins detect pathogens

Alessandra Cambi,1 Marjolein Koopman2 and Carl G. Figdor*1

1Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Radboud University, Nijmegen, the Netherlands.
2Applied Optics Group, Faculty of Science and Technology and MESA+ Institute for Nanotechnology, University of Twente, Enschede, the Netherlands.

Summary

Glycosylation of proteins has proven extremely important in a variety of cellular processes, including enzyme trafficking, tissue homing and immune functions. In the past decade, increasing interest in carbohydrate-mediated mechanisms has led to the identification of novel carbohydrate-recognizing receptors expressed on cells of the immune system. These non-enzymatic lectins contain one or more carbohydrate recognition domains (CRDs) that determine their specificity. In addition to their cell adhesion functions, lectins now also appear to play a major role in pathogen recognition. Depending on their structure and mode of action, lectins are subdivided in several groups. In this review, we focus on the calcium (Ca$^{2+}$)-dependent lectin group, known as C-type lectins, with the dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN) as a prototype type II C-type lectin organized in microdomains, and their role as pathogen recognition receptors in sensing microbes. Moreover, the cross-talk of C-type lectins with other receptors, such as Toll-like receptors, will be discussed, highlighting the emerging model that microbial recognition is based on a complex network of interacting receptors.

Introduction

Classical C-type lectins contain so-called carbohydrate recognition domains (CRDs) that bind carbohydrate structures in a calcium (Ca$^{2+}$)-dependent manner. Ca$^{2+}$ ions are directly involved in both ligand binding as well as in maintaining the structural integrity of the CRD that is necessary for the lectin activity (Drickamer, 1999). C-type lectins contain a prototypic lectin fold, consisting of two anti-parallel β-strands and two α-helices (Weis et al., 1991). The C-type CRDs form a subfamily of the larger group of protein domains called C-type lectin-like domains (CTLDs). Some CTLDs bind protein or lipid moieties instead of carbohydrates; often these are Ca$^{2+}$-independent. However, there have been examples described of Ca$^{2+}$-independent carbohydrate binding (Drickamer, 1999; Kogelberg and Feizi, 2001). CTLDs containing receptors are also indicated as C-type lectin-like receptors (CLRs).

C-type lectins are either produced as transmembrane proteins or secreted as soluble proteins (Table 1). Examples of soluble C-type lectins include members of the collectins family (Lu et al., 2002), such as the lung surfactant proteins A (SP-A) and SP-D (Wintergest et al., 1989), which are secreted at the luminal surface of pulmonary epithelial cells, and the mannose-binding protein (MBP), a collectin present in the plasma (Kawasaki et al., 1983).

Transmembrane C-type lectins can be divided into two groups, depending on the orientation of their amino (N)-terminus. These are type I and type II C-type lectins depending on their N-terminus pointing outwards or inwards into the cytoplasm of the cell respectively.

Examples of transmembrane C-type lectins are the selectins (Ley and Kansas, 2004), the mannose receptor (MMR) family (East and Isacke, 2002), and the dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN) (Geijtenbeek et al., 2000a).

In the immune system, C-type lectins and CLRs have been shown to act both as adhesion and as pathogen recognition receptors (Cambi and Figdor, 2003). While cell–cell contact is a primary function of selectins, other C-type lectins, like collectins, are specialized in recognition of pathogens (Table 1). Interestingly, DC-SIGN is a cell adhesion receptor as well as a pathogen recognition receptor. As adhesion receptor, DC-SIGN mediates the contact between dendritic cells (DCs) and T lymphocytes, by binding to ICAM-3 (Geijtenbeek et al., 2000a), and...
The defence against microbes is based on the ability of the innate immune system to recognize conserved microbial components that are specific to the microorganisms. These components are highly conserved and referred to as PAMPs. Examples of PAMPs include the Gram-negative bacteria lipopolysaccharide (LPS), the Gram-positive bacteria peptidoglycans and fungus cell wall polysaccharides (Teixeira et al., 2002).

The capacity of C-type lectins to sense microorganisms is highly dependent on the density of the PAMP present on the microbial surface as well as on the degree of multimerization of the lectin receptor. In fact, the arrangement of several CRDs in multimers projects the binding sites in a common direction, in order to allow interactions with the arrays of carbohydrates on microbial surfaces.

The soluble collectins form trimers that may further assemble into larger oligomers. Mutations that compromise assembly of higher-order oligomers of the human MBL have been shown to result in reduced capability to activate components of the complement system. This increases both risk and severity of infections and can even lead to autoimmunity (Larsen et al., 2004). Moreover, the assembly of SP-D trimers into dodecamers seems required for the proper regulation of surfactant phospholipid homeostasis and the prevention of emphysema (Zhang et al., 2001).

Table 1. Overview of structural and functional relationships of subfamilies of C-type lectins involved in pathogen sensing.

| Group and molecular structure | C-type lectin | Pathogen | Ligand specificity |
|------------------------------|---------------|----------|--------------------|
| MMR family                   | MMR           | HIV, Pneumocystis, Mycobacterium tuberculosis, C. albicans | Mannose, fucose, sLe\(^{\text{a(b)}}\) |
| DEC-205                      | Endo-180      | Unknown  | Unknown            |
| Collectins                   | MBL           | HIV, IAV, Staphylococcus aureus, Streptococcus pneumoniae, C. albicans, Aspergillus fumigatus | GlcNAc, ManNAc, fucose, glucose |
| SP-A                         | SP-D          | IAV, RSV, HIV-1, S. aureus, S. pneumoniae, A. fumigatus | ManNAc, fucose, glucose, GlcNAc |
| Type II receptors            | DC-SIGN       | HIV, HCV, CMV, Dengue, H. pylori, M. tuberculosis, S. mansoni, C. albicans, A. fumigatus, Leishmania | Mannan, Le\(^{\text{a}}\), Le\(^{\text{b}}\), Le\(^{\text{c}}, \text{SLen, ManLam}\) |
| L-SIGN                       | Unknown       | Unknown  | Unknown            |
| DCIR                         | Langerin      | Unknown  | Unknown            |
| DCAL-1                       | BDCA-2        | Unknown  | Unknown            |
| NK receptors                 | β-GR (Dectin-1)| Pneumocystis, C. albicans | β-Glucan |
| CLEC-1                       | Unknown       | Unknown  | Unknown            |
| CLEC-2                       | Unknown       | Unknown  | Unknown            |

(a). Based on nomenclature http://ctld.glycob.ox.ac.uk
(b). This interaction occurs through the cystein-rich domain, not the CRD, of the MMR.

© 2005 Blackwell Publishing Ltd, Cellular Microbiology, 7, 481–488
Also transmembrane C-type lectins have developed several strategies to increase the interaction strength with PAMPs.

The extracellular portion of the MMR is composed of several CRDs, of which at least three are required for high-affinity binding and endocytosis of multivalent glycoconjugates. Thus, several CRDs with only weak affinity for single carbohydrates are clustered in one single molecule to achieve higher-affinity binding (Taylor et al., 1992).

Biochemical studies using soluble recombinant fragments of DC-SIGN and its liver homologue L-SIGN indicate that the extracellular domain of each molecule is a tetramer stabilized by an α-helical neck and that the individual CRDs have high affinity for mannose-containing oligosaccharides (Mitchell et al., 2001). Recently, we observed that DC-SIGN can be expressed in different levels of organization (clustering) on DCs cell surface, depending on their differentiation state when developed from monocyte precursors (Cambi et al., 2004). High-resolution electron microscopy (EM) images demonstrated a direct relation between DC-SIGN function as viral receptor and its microlocalization on the plasma membrane. During development of human monocyte-derived DCs, DC-SIGN molecules distribution alters from a random-distribution pattern into well-defined microdomains on the cell membrane (Fig. 1). These microdomains have an average diameter of 100–200 nm, as established by EM and Near-field Scanning Optical Microscopy (Koopman et al., 2004). The organization of DC-SIGN in microdomains on the plasma membrane is important for binding and internalization of virus particles, suggesting that these multimolecular assemblies of DC-SIGN act as a docking site for pathogens like HIV-1 to invade the host (Cambi et al., 2004).

A clustered localization on the microvilli of human lymphocytes has also been documented for selectins, C-type lectins which play a major role in cell adhesion but are not involved in pathogen recognition (Hasslen et al., 1995). The clustered distribution of L-selectin was suggested to facilitate the rolling of lymphocytes on the endothelial surface (Hasslen et al., 1995). Moreover, the P-selectin homodimer has unique functional characteristics compared with its monomeric form, and dimerization occurs in the endoplasmic reticulum and Golgi compartments of endothelial cells (Barkalow et al., 2000).

C-type lectins specificity is a consequence of subtle differences in ligand glycosylation

Recent findings reported by several investigators indicate that CLR s recognize subtle differences in the arrangement and branching of the carbohydrate residues. For example, MMR recognizes end-standing single mannose moieties, whereas DC-SIGN has higher affinity for more complex mannose residues in specific arrangements (Mitchell et al., 2001). Despite the fact that several of the C-type lectins 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. A good example is the different modifications of Lewis blood-group antigen that bind to completely different C-type lectins (Cambi and Figdor, 2003). In fact, while DC-SIGN recognizes the unsialylated form of Lewis-X and Lewis-A (Appelmelk et al., 2003), P- and E-selectin have high affinity for sialylated Lewis-X and Lewis-A (Fukuda et al., 1999). In addition, both E- and L-selectin have been shown to interact with sulphated forms of Lewis-X and Lewis-A (Green et al., 1992; Yuen et al., 1992), while DC-SIGN strongly binds to sulphated Lewis-A but not to sulphated Lewis-X (Appelmelk et al., 2003). The MMR does interact with sulphated oligosaccharides of Lewis-X, but this interaction occurs via the cysteine-rich domain rather than the CRD (Leteux et al., 2000).

The complexity of carbohydrate structures and the need to establish binding specificity for C-type lectins stimulated

Fig. 1. The C-type lectin DC-SIGN is organized in microdomains on the cell surface of immature DCs. A. The cell surface distribution of DC-SIGN on the cell membrane was visualized by transmission EM on whole-mount sample of immature DCs specifically labelled with 10 nm immunogold beads (A’). Scale bar 100 nm. B. The organization into microdomains was confirmed by imaging of fluorescent anti-DC-SIGN antibody on immature DC, using NSOM under liquid conditions. By NSOM, the fluorescence signal is collected simultaneous with the cell topography (very high parts are white in the topography image. The bright spots (B’) correspond to DC-SIGN microdomains, while the topography allows 3D mapping of domain organization on the cell surface. The scale bar in the NSOM image is 200 nm.
the development of several techniques to decipher the ‘glyco-code’.

Oligosaccharide clusters are chemically defined compounds that have been used in combination with surface plasmon resonance to identify ligands selectively recognized by various C-type lectins. In particular, mannoside clusters have been shown to be recognized by the MMR with high affinity and by DC-SIGN with very low affinity; conversely, Lewis clusters show higher affinity for DC-SIGN than for the MMR (Frison et al., 2003).

Alternatively, glycodendrimers, based on a hyperbranched polymer functionalized with different carbohydrates, have been used to interfere with biological processes where carbohydrates are involved. For example, mannosyl glycodendritic structures have been used to inhibit DC-SIGN-mediated infection of Ebola virus in cis and in trans (Lasala et al., 2003).

Soluble chimeric DC-SIGN–IgG1-Fc fusion proteins have been used in an ELISA format to screen for a panel of synthetic glycoconjugates containing mannose or fucose. This allowed the identification of new distinct carbohydrate structures that interact with DC-SIGN. Based on this information, it could be predicted that pathogens could be recognized by this receptor (Appelmelk et al., 2003).

Identification of carbohydrate moieties specific for particular lectins provide new perspectives for the design and development of drugs to prevent (chronic) infections by pathogens. Therapeutic manipulations of carbohydrate–protein interactions require detailed knowledge of the specific spectrum of carbohydrate structures recognized by each lectin. Oligosaccharide microarray technologies are currently developed to facilitate a more rigorous, systematic and high-throughput analysis of protein–carbohydrate interactions.

One of the best examples is the neoglycolipid technology that generates lipid-linked oligosaccharide arrays from glycoproteins, glycolipids, proteoglycans, polysaccharides, whole organs or chemically synthesized oligosaccharides (Feizi and Chai, 2004). By glycan array profiling discrimination of high- and low-affinity carbohydrate ligands for the murine C-type lectins SIGN-R1, SIGN-R3 and langerin have been determined (Galustian et al., 2004).

Alternative glycan arrays are also documented. Recently, Guo et al. (2004) showed that DC-SIGN and its homologue L-SIGN have distinct ligand-binding properties. While L-SIGN was only able to bind to mannose-containing ligands, DC-SIGN reacted with many more glycans, including those containing blood group antigens (Guo et al., 2004). The observation that DC-SIGN and L-SIGN differ in their carbohydrate binding profiles was also demonstrated by the work of Van Limpt et al. (2004). By examining Schistosoma mansoni egg antigen and various mutants of DC-SIGN and L-SIGN, they demonstrated that the difference in one single amino acid at the binding site is responsible for the fucose specificity of DC-SIGN (van Limpt et al., 2004).

Detailed knowledge of the carbohydrate specificity of this family of receptors will contribute to the further understanding of the functional roles of the C-type lectins in glycan recognition of pathogens and carbohydrates expressed at the cell surface.

Antigen uptake by C-type lectins

The main function of C-type lectins in microbial recognition is binding and subsequent internalization for direct elimination by macrophages. At the same time, lysosomal degradation produces antigenic fragments that after presentation by DCs and macrophages in MHC molecules at the cell surface stimulate the adaptive immune system (Fidgory et al., 2002).

Besides the classical MMR, which is known to act as an endocytic receptor, DEC-205 (Mahnke et al., 2000) and DC-SIGN (Engering et al., 2002; Cambi et al., 2003; Ludwig et al., 2004) have also recently been demonstrated to mediate antigen uptake. Interestingly, on DCs, we observed that the fungus Candida albicans was internalized in vesicles containing both MMR and DC-SIGN as well as in mutually exclusive vesicles (Fig. 2). It would be interesting to characterize these vesicles in more details and to elucidate whether the destiny of the C. albicans containing vesicles enriched in DC-SIGN is different from those enriched in MMR.

While the MMR delivers antigens to the early endosomes and recycles to the surface, DEC-205 and DC-SIGN deliver antigens to late endosomes or lysosomes where they are degraded. Besides the tyrosine based coated pit sequence uptake motif present in MMR, the cytoplasmic domains of DEC-205 and DC-SIGN contain an additional triacidic cluster important for targeting to proteolytic vacuoles (Mahnke et al., 2000). Furthermore, a dileucine motif present in the cytoplasmic domain of DC-SIGN is essential for internalization (Engering et al., 2002).

The liver sinusoidal endothelial cell (LSEC)-associated homologue of DC-SIGN – here designated as L-SIGN – is not expressed by DCs (Bashirova et al., 2001). Liver sinusoids are specialized capillary vessels characterized by the presence of resident macrophages adhering to the LSECs. The LSEC–leukocyte interactions, which require expression of adhesion molecules on the cell surfaces, appear to constitute a central mechanism of peripheral immune surveillance in the liver. MMR and now also L-SIGN are known to be expressed on LSECs and may mediate the clearance of many potentially antigenic proteins from the circulation, in a manner similar to DC in lymphoid organs.

© 2005 Blackwell Publishing Ltd, Cellular Microbiology, 7, 481–488
Whether L-SIGN is able to internalize antigen remains controversial. Ludwig et al. (2004) demonstrated that hepatitis C virus particles are internalized by monocytic cell line transfected with L-SIGN and target non-lysosomal compartments to escape degradation. In contrast, Guo et al. (2004) showed that L-SIGN expressed in fibroblasts is not able to release its ligands at low pH and does not mediate endocytosis, suggesting that L-SIGN predominantly acts as an adhesion receptor. Investigating the internalization capacity of DC-SIGNR on a more physiological context (i.e. on LSECs) might shed some light on this controversial issue.

C-type lectins and Toll-like receptors cross-talk

Besides C-type lectins, Toll-like receptors (TLRs) are also involved in the direct recognition of specific PAMPs on immune cells, particularly DCs and macrophages (Takeda et al., 2003). While the main function of C-type lectins is to internalize antigens for degradation in order to enhance antigen processing and presentation (Figdor et al., 2002), TLRs recognize foreign carbohydrate structures and trigger intracellular signalling cascades that lead to the production of proinflammatory cytokines, thus causing T cell activation (Takeda et al., 2003).

Fig. 2. The C-type lectins DC-SIGN and MMR are the major player in the internalization of C. albicans by immature DCs. Immature DCs were incubated with live FITC-labelled C. albicans conidia (green) for 30 min at 37°C, fixed, permeabilized and labelled with anti-MMR (red) or anti-DC-SIGN (blue) antibodies and subsequently with isotype-specific Alexa-conjugated secondary antibodies. The fungus C. albicans is internalized by immature DCs in vesicles containing both MMR and DC-SIGN (white arrow head) as well as in mutually exclusive vesicles (white arrows). Scale bar is 10 µm.

Increasing evidence suggests that TLRs and C-type lectins communicate with each other, and that this cross-talk is critically important for the balance between immune tolerance and immune activation. In particular, the β-glucans receptor, Dectin-1, has been shown to mediate binding and to phagocytose yeast and fungal-derived zymosan, resulting in the production of inflammatory cytokines by macrophages (Brown et al., 2003). Interestingly, TLR-2 and TLR-6 are also responsible for the production of zymosan-induced inflammatory cytokines (Takeda et al., 2003). Dectin-1 colocalizes with both TLR-2 and TLR-6 in areas of contact between zymosan particles and macrophages and its increased expression significantly enhanced TLR-2 depending zymosan-induced tumour necrosis factor alpha (TNFα) production (Brown et al., 2003).

In contrast, mycobacterium-derived mannosylated lipoarabinomannans (ManLAM) have been shown to bind to DCs via DC-SIGN, thereby inhibiting TLR-mediated IL-12 production and stimulating IL-10 production (Geijtenbeek et al., 2003). Blocking antibodies against DC-SIGN were able to restore IL-12 production, demonstrating that ManLAM triggers anti-inflammatory signalling via DC-SIGN (Geijtenbeek et al., 2003). These observations suggest that simultaneous binding of mycobacterium compo-
ments to DC-SIGN and TLRs might skew the immune system from a protective Th1 response towards a tolerogenic Th2 response, thus facilitating immune escape of mycobacteria. Along the same line, the collectin SP-A has been shown to downregulate zymosan-induced signalling and TNFα production by attenuating the binding of TLR-2 to zymosan (Sato et al., 2003).

Therefore, a model emerges in which microbial recognition is not the result of one microbial component interacting with a single recognition receptor, but a complex network of interacting receptors and ligands. Depending on the type of the receptors involved, and also the organization of the receptors at the cell surface, the outcome can be completely different. It can result in simple resolution of the pathogen but also lead to a vigorous adaptive immune response or lead to tolerance induction.

C-type lectins and lipid rafts

Lipid rafts are localized regions with elevated cholesterol and glycosphingolipid content that can be found on the plasma and endosomal membrane of eukaryotic cells and act as signalling platforms (Simons and Toomre, 2000). Several studies have demonstrated that some microbial pathogens exploit cholesterol enriched lipid microdomains as docking sites to enter host cells. Some viruses, such as HIV-1, appear to target lipid raft microdomains during viral entry into cells, as well as during viral assembly (Dimitrov, 1997; Mañes et al., 2000). Other studies suggest that cholesterol-dependent membrane properties, rather than lipid rafts per se, are responsible to promote efficient HIV-1 infection in T cells (Percherancier et al., 2003).

On the cell membrane of DCs, we investigated the relation between DC-SIGN organized in microdomains and the lipid rafts (Cambi et al., 2004). Biochemical studies showed that a significant portion of DC-SIGN resides in detergent-resistant membrane fraction, where lipid rafts can also be found. In addition, colocalization of DC-SIGN with the lipid raft marker GM1 was observed by confocal as well as electron microscopy. However, disruption of lipid rafts by cholesterol extraction did not alter the integrity of DC-SIGN microdomains, suggesting the existence of additional molecular determinants that regulate the association of a trans-membrane protein, like DC-SIGN, with lipid rafts (Cambi et al., 2004). Nevertheless, the localization of DC-SIGN in these lipid microdomains may create a scaffold that favours pathogen binding as well as allow the interaction of DC-SIGN with signalling molecules that are also recruited into the same membrane domains.

Another example of C-type lectin colocalizing with lipid rafts is E-selectin. To date, no involvement of this receptor in pathogen recognition has been documented. E-selectin is an endothelial cell surface adhesion molecule for leukocytes rolling and also acts as a signalling receptor. Upon antibody triggering, E-selectin was found to partition in detergent-insoluble portion of the endothelial cellular lysate together with ICAM-1 (Tilghman and Hoover, 2002). Moreover, the presence of E-selectin in lipid rafts proved to be mandatory for its association with, and activation of, PLCγ, suggesting that this subcellular localization of E-selectin is important for its signalling function(s) during leukocyte–endothelial interactions (Kiely et al., 2003).

We have already mentioned that cross-talk between C-type lectins and TLRs controls the toggle between tolerogenic and activating immune responses. Recently, both TLR-2 and TLR-4 have also been shown to be recruited into lipid rafts (Triantafilou et al., 2002; Soong et al., 2004). At the apical surface of airway epithelial cells, TLR-2 is enriched in caveolin-1-associated lipid raft microdomains after bacterial infection and its signalling capabilities are amplified by its association with the lipid raft ganglioside GM1 (Soong et al., 2004). TLR-4 was found to mobilize into lipid rafts together with other bacterial recognition immune receptors (such as CD-14) upon LPS-induced cell activation (Triantafilou et al., 2002). The observation that several C-type lectins and some TLRs may associate within lipid rafts suggests the possibility of spatially confined interactions between these two families of receptors. Especially for those C-type lectins lacking signalling motifs in their cytoplasmic domain, residing in a signalling platform such as a lipid raft increases their chance to activate components of the cell’s endogenous signalling machinery.

Conclusions

During the past few years a wealth of information has become available illustrating the importance of the C-type lectins especially for the proper functioning of the immune system. However, the emerging picture indicates that microbial recognition must be based on networking between C-type lectins and other innate immune recognition receptors. Unravelling the precise signalling mechanisms regulating these interactions is the present challenge. Novel techniques such as multiphoton laser microscopy and high-resolution fluorescence microscopy will certainly reveal the dynamics in time and space of immune receptors like C-type lectins and TLRs during pathogen recognition.

Acknowledgements

A.C. is supported by Grant SLW 33.302P from the Netherlands Organization of Scientific Research, Earth and Life Sciences. M.K. is supported by the Netherlands Foundation for Fundamental Research of Matter (FOM), which is financially supported by NWO. C.G.F. is supported by Grant NWO 901-10-092.

© 2005 Blackwell Publishing Ltd, Cellular Microbiology, 7, 481–488
resolution single molecule detection on dendritic cells.

FEBS Lett 573: 6–10.

Lasala, F., Arce, E., Otero, J.R., Rojo, J., and Delgado, R. (2003) Mannosyl glycodendritic structure inhibits DC-SIGN-mediated Ebola virus infection in cis and in trans. Antimicrob Agents Chemother 47: 3970–3972.

Larsen, F., Madsen, H.O., Sim, R.B., Koch, C., and Garred, P. (2004) Disease-associated mutations in human mannose-binding lectin compromise oligomerization and activity of the final protein. J Biol Chem 279: 21302–21311.

Leteux, C., Chai, W., Loveless, R.W., Yuen, C.T., Uhlin-Hansen, L., Combarroues, Y., et al. (2000) The cytokine-rich domain of the macrophage mannose receptor is a multispecific lectin that recognizes chondroitin sulfates A and B and sulfated oligosaccharides of blood group Lewis(a) and Lewis(x) types in addition to the sulfated N-glycans of lutropin. J Exp Med 191: 1117–1126.

Ley, K., and Kansas, G.S. (2004) Selectins in T-cell recruitment to non-lymphoid tissues and sites of inflammation. Nat Rev Immunol 4: 325–335.

Lozach, P.Y., Lortat-Jacob, H., De Lacroix De Lavallade, A., Staropoli, I., Foug, S., Amara, A., et al. (2003) DC-SIGN and L-SIGN are high-affinity binding receptors for hepatitis C virus glycoprotein E2. J Biol Chem 278: 20358–20366.

Lu, J., Teh, C., Kishore, U., and Reid, K.B.M. (2002) Collectins and ficolins: sugar pattern recognition molecules of the mammalian innate immune system. Biochim Biophys Acta 1572: 387–400.

Ludwig, I.S., Lekkerkerker, A.N., Depla, E., Bosman, F., Musters, R.J., Depaere, S., et al. (2004) Hepatitis C virus targets DC-SIGN and L-SIGN to escape lysosomal degradation. J Virol 78: 8322–8332.

Mahnke, K., Guo, M., Lee, S., Sepulveda, H., Swain, S.L., Nussenzweig, M., and Steinman, R.M. (2000) The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II-positive lysosomal compartments. J Cell Biol 151: 673–684.

Mahes, S., del Real, G., Lacalle, R.A., Lucas, P., Gomez-Mouton, C., Sanchez-Palomin, S., et al. (2000) Membrane raft microdomains mediate lateral assemblies required for HIV-1 infection. EMBO Rep 1: 190–196.

Mitchell, D.A., Fadden, A.J., and Drickamer, K. (2001) A novel mechanism of carbohydrate recognition by the C-type lectins DC-SIGN and DC-SIGNR. J Biol Chem 276: 28939–28945.

Nguyen, D.G., and Hildreth, J.E. (2003) Involvement of macrophage mannose receptor in the binding and transmission of HIV by macrophages. Eur J Immunol 33: 483–493.

Percherancier, Y., Lagane, B., Planchenuit, S., Staropoli, I., Altmeier, R., Virelleizer, J.L., et al. (2003) HIV-1 entry into T-cells is not dependent on CD4 and CCR5 localization to sphingolipid-enriched, detergent-resistant, raft membrane domains. J Biol Chem 278: 3153–3161.

Sato, M., Sano, H., Iwaki, D., Kudo, K., Konishi, M., Takanhashi, H., et al. (2003) Direct binding of Toll-like receptor 2 to zymosan, and zymosan-induced NF-kappa B activation and TNF-alpha secretion are down-regulated by lung collectrin surfactant protein A. J Immunol 171: 417–425.

Simons, K., and Toomre, D. (2000) Lipid rafts and signal transduction. Nat Rev Mol Cell Biol 1: 31–39.

Soong, G., Reddy, B., Sokol, S., Adamo, R., and Prince, A. (2004) TLR2 is mobilized into an apical lipid raft receptor complex to signal infection in airway epithelial cells. J Clin Invest 113: 1482–1489.

Takeda, K., Kaisho, T., and Akira, S. (2003) Toll-like receptors. Annu Rev Immunol 21: 335–376.

Taylor, M.E., Bezoukga, K., and Drickamer, K. (1992) Contribution to ligand binding by multiple carbohydrate-recognition domains in the macrophage mannose receptor. J Biol Chem 267: 1719–1726.

Teixeira, M.M., Almeida, I.C., and Gazzinelli, R.T. (2002) Introduction: innate recognition of bacteria and protozoan parasites. Microbes Infect 4: 883–886.

Tilghman, R.W., and Hoover, R.L. (2002) E-selectin and ICAM-1 are incorporated into detergent-insoluble membrane domains following clustering in endothelial cells. FEBS Lett 525: 83–87.

Triantafilou, M., Miyake, K., Golenbock, D.T., and Triantafilou, K. (2002) Mediators of innate immune recognition of bacteria concentrate in lipid rafts and facilitate lipopolysaccharide-induced cell activation. J Cell Sci 115: 2603–2611.

Van Die, I., van Vliet, S.J., Nyame, A.K., Cummings, R.D., Bank, C.M., Appelmelk, B., et al. (2003) The dendritic cell specific C-type lectin DC-SIGN is a receptor for Schistosoma mansoni egg antigens and recognizes the glycan antigen Lewis-x. Glyobiology 13: 471–478.

Van Liempt, E., Immerty, A., Bank, C.M., Van Vliet, S.J., Van Kook, Y., Geijtenbeka, T.B., and Van Die, I. (2004) Molecular basis of the differences in binding properties of the highly related C-type lectins DC-SIGN and L-SIGN to Lewis X triasaccharide and Schistosoma mansoni egg antigens. J Biol Chem 279: 33161–33167.

Weis, W.I., Kahn, R., Fournet, R., Drickamer, K., and Hendrickson, W.A. (1991) Structure of the calcium-dependent lectin domain from a rat mannose-binding protein determined by MAD phasing. Science 254: 1608–1615.

Wintergast, E., Manz-Keinke, H., Plattner, H., and Schlepper-Schafer, J. (1989) The interaction of a lung surfactant protein (SP-A) with macrophages is mannose dependent. Eur J Cell Biol 50: 291–298.

Yuen, C.T., Lawson, A.M., Chai, W., Larkin, M., Stoll, M.S., Stuart, A.C., et al. (1992) Novel sulfated ligands for the cell adhesion molecule E-selectin revealed by the neoglycolipid technology among O-linked oligosaccharides on an ovian cystadenoma glycoprotein. Biochemistry 31: 9126–9131.

Zhang, L., Igemami, M., Crouch, E.C., Korthagen, T.R., and Whitsett, J.A. (2001) Activity of pulmonary surfactant protein-D (SP-D) in vivo is dependent on oligomeric structure. J Biol Chem 276: 19214–19219.