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Microreview

How C-type lectins detect pathogens

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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 antiparallel 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 $Ca2^{+}$ independent. However, there have been examples described of $Ca2^{+}$-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).

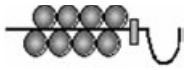
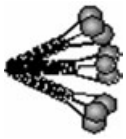
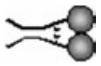
Transmembrane C-type lectins can be divided into two groups, depending on the orientation of their amino (N)-terminus. These are type I and type II C-type lectins depending on their N-terminus pointing outwards or inwards into the cytoplasm of the cell respectively.

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

Received 10 November, 2004; accepted 16 December, 2004. *For correspondence. E-mail: c.figdor@ncmls.ru.nl; Tel. (+31) 24 3617600; Fax (+31) 24 3540339.

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

Group and molecular structure[(a)]	C-type lectin	Pathogen	Ligand specificity
MMR family 	MMR	HIV, *Pneumocystis*, *Mycobacterium tuberculosis*, *C. albicans*	Mannose, fucose, sLe^{x}[(b)]
	DEC-205	Unknown	Unknown
	Endo-180	Unknown	Collagen, mannose, fucose, GlcNAc
Collectins 	MBL	HIV, IAV, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *C. albicans*, *Aspergillus fumigatus*	GlcNAc, ManNAc, fucose, glucose
	SP-A	IAV, RSV, HSV-1, *S. aureus*, *S. pneumoniae*, *A. fumigatus*	ManNAc, fucose, glucose, GlcNAc
	SP-D	IAV, RSV, *M. tuberculosis*, *Pseudomonas aeruginosa*, *A. fumigatus*, *C. albicans*	Maltose, mannose, glucose, lactose, galactose, GlcNAc
Type II receptors 	DC-SIGN	HIV, HCV, CMV, Dengue, *H. pylori*, *M. tuberculosis*, *S. mansoni*, *C. albicans*, *A. fumigatus*, *Leishmania*	Mannan, Le^{X}, Le^{a}, Le^{y}, Le^{b}, SLe^{a}, ManLam
	L-SIGN	HIV, HCV, *S. mansoni*	Mannan, Le^{a}, Le^{y}, Le^{b}
	DCIR	Unknown	Unknown
	Langerin	Unknown	Mannose, GlcNAc, fucose, $6SLe^{X}$
	DCAL-1	Unknown	Unknown
	BDCA-2	Unknown	Unknown
NK receptors 	β-GR (Dectin-1)	*Pneumocystis*, *C. albicans*	β-Glucan
	CLEC-1	Unknown	Unknown
	CLEC-2	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.

C-type lectin domain; fibronectin type II repeat; collagen-like triple helix.

IAV, influenza A virus; RSV, respiratory syncytial virus; HSV-1, herpes simplex virus type 1; β-GR, β-glucan receptor; GlcNAc, N-acetyl-D-glucosamine; ManNAc, N-acetyl-D-mannosamine; ManLAM, mannosyl-lipoarabinomannan; Le^{a}, LewisA; Le^{b}, LewisB, Le^{y}, LewisY; $6SLe^{X}$, 6-sulpho sialyl-$Lewis^{X}$.

mediates rolling of DCs on endothelium, by interacting with ICAM-2 (Geijtenbeek *et al*., 2000b). As pathogen uptake receptor, DC-SIGN recognizes a variety of microorganisms, including viruses (Geijtenbeek *et al*., 2000c; Klimstra *et al*., 2003; Lozach *et al*., 2003), bacteria (Geijtenbeek *et al*., 2003), fungi (Cambi *et al*., 2003) and several parasites (Colmenares *et al*., 2002; Van Die *et al*., 2003). Recently, the type I CLR MMR, mainly known as pathogen recognition receptor (Ezekowitz *et al*., 1990; Nguyen and Hildreth, 2003), was discovered to mediate adhesion between human lymphatic endothelium and lymphocytes through L-selectin (Irjala *et al*., 2001).

In this review, we shall focus on the role of C-type lectins in the recognition of pathogens, discussing their binding specificity as a consequence of differences in ligand glycosylation, the molecular and structural determinants that regulate the interaction with pathogen-associated molecular patterns (PAMPs), and finally the cross-talk with other membrane receptors that mediate signalling and internalization events.

C-type lectin multimerization

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).

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).

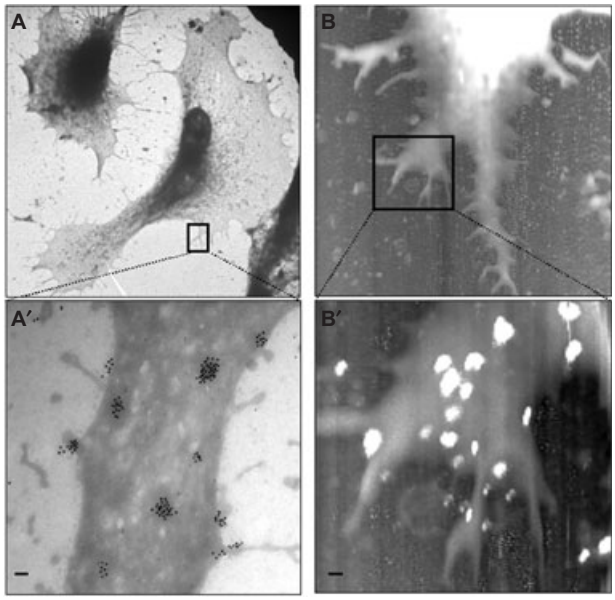


Fig. 1. The C-type lectin DC-SIGN is organized in microdomains on the cell surface of immature DCs.
A. The cell surface distribution of DC-SIGN on the cell membrane was visualized by transmission EM on whole-mount sample of immature DCs specifically labelled with 10 nm immunogold beads (A′). Scale bar 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.

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

Recent findings reported by several investigators indicate that CLRs 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

the development of several techniques to decipher the 'glyco-code'.

Oligolysine-based 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, dimannoside 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 Liempt *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 Liempt *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 pathogen 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 (Figdor *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 antigen 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.

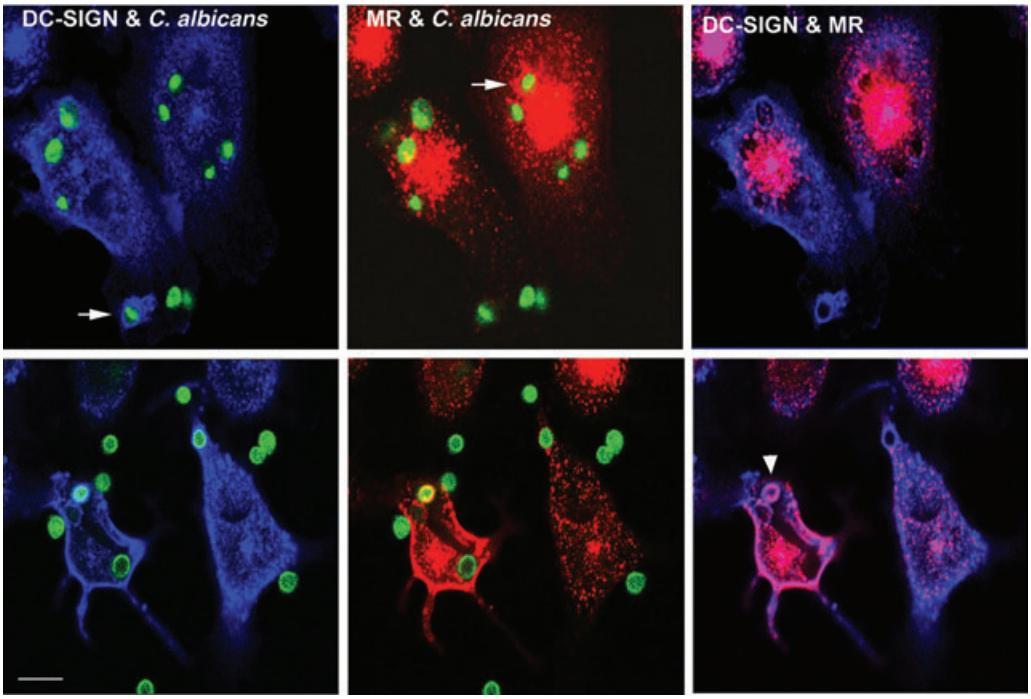


Fig. 2. The C-type lectins DC-SIGN and MMR are the major player in the internalization of *C. albicans* by immature DCs. Immature DCs were incubated with live FITC-labelled *C. albicans* conidiae (green) for 30 min at 37°C, fixed, permeabilized and labelled with anti-MMR (red) or anti-DC-SIGN (blue) 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.

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 compartements 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).

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-

nents 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

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