Chapter 17
C-Type Lectin Receptors

Nobuo Kanazawa

Abstract C-type lectins, originally defined as proteins binding carbohydrates in a Ca^{2+}-dependent manner, form a large family containing soluble and membrane-bound proteins. Among them, those expressed on phagocytes and working as pathogen pattern-recognition receptors were designated as C-type lectin receptors (CLRs), in accordance with Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I–like receptors (RLRs). Most of the genes for CLRs are clustered in human chromosome 12 close to the natural killer gene complex. Similar to the killer lectin-like receptors whose genes are clustered in this complex, most of the CLRs induce activating or regulatory signal cascades in response to distinct pathogen- or self-derived components, through the immunoreceptor tyrosine-based activating or inhibitory motif, respectively. In this chapter, some representative CLRs are picked up and their structural features leading to the functional consequences are discussed, especially on the signaling cascades and pathogen interactions, including some impacts on cutaneous pathophysiology. These CLRs should provide targets to develop effective vaccination and therapeutics for distinct infectious and autoimmune/inflammatory diseases.

**Keywords** CARD9 • CLEC • CLR • DC • FcRγ • ITAM • LC • pDC • Syk

17.1 Overview

C-type lectin (CTL) was originally defined as a protein that binds carbohydrate in a Ca^{2+}-dependent manner [105]. CTLs form a large family containing soluble and membrane-bound proteins and the family members share a common domain structure named the carbohydrate recognition domain (CRD), which consists of 18 highly conserved amino acid residues including two folds of disulfide bonds formed by four cysteine residues [20]. However, not all of the structurally related CRDs have been shown to bind Ca^{2+} or carbohydrates, and the term C-type lectin-like domain (CTLD) has been designated for the domain without Ca^{2+}-dependent

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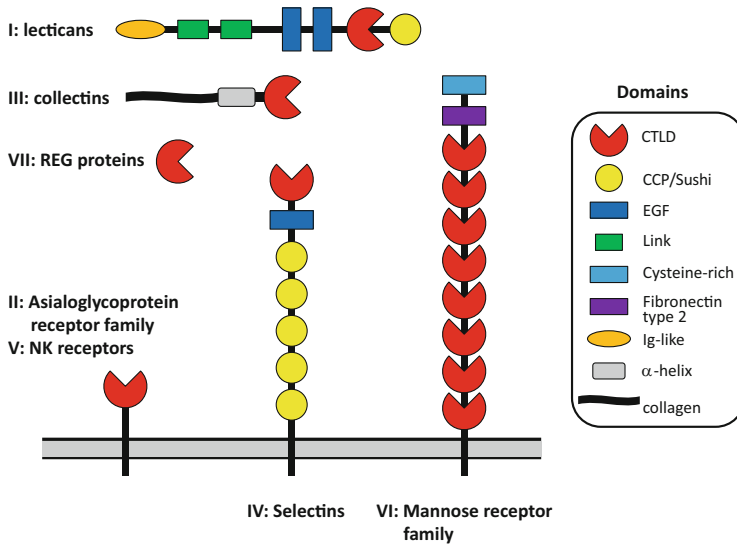
Fig. 17.1 Domain structure for the traditional seven (I–VII) groups of vertebrate CTLs. Domain names are listed in the box

sugar-binding capacity, whose amino acid sequence shows incomplete conservation of the common residues in the CRD [22]. It should be noted that the term CTLD is also used for the broad definition containing all CTLs irrespective of carbohydrate recognition [116].

Based on the domain structure, vertebrate CTLs were divided into 7 (I–VII) or, more recently, 17 (I–XVII) groups including the traditional seven groups [58, 116]. Among them, group I (lecticans: aggrecan, brevican, versican, and neurocan), III (collectins: mannose-binding protein and pulmonary surfactant proteins), and VII (Reg proteins) are soluble, whereas group II (asialoglycoprotein receptor family), IV (selectins), V (natural killer receptor family), and VI (mannose receptor family) are bound to the cell membrane (Fig. 17.1).

The natural killer (NK) receptor family (group V) contains a series of type II transmembrane proteins with a single CTLD expressed on NK cells, whose genes are clustered in the NK gene complex (NKC) in chromosome 12 [113]. They are collectively called killer lectin-like receptors (KLRs) and are equipped to regulate the killer activity of their expressing cells. Among them, heterodimers of CD94 and activating/inhibitory NKG2 receptors, as well as the activating NKG2D homodimer, recognize major histocompatibility complex (MHC) class I or related molecules, to distinguish target cells appropriately. The CTLDs included in these receptors have no capacity to bind carbohydrate.

Phagocytes, such as macrophages and dendritic cells (DCs), also express various kinds of CTL receptors on their cell surface for antigen capture. The mannose receptor (MR) family (group VI) contains type I transmembrane proteins with multiple CTLDs, such as the MR (CD206) and DEC-205 (CD205) [27]. They

commonly consist of an N-terminal cysteine-rich domain and a fibronectin type II domain as well as eight or ten CTLDs. In contrast, the asialoglycoprotein receptor family (group II) contains type II transmembrane proteins with a single CTLD, such as DC-specific ICAM3-grabbing nonintegrin (DC-SIGN, CD209), dectin-1, dectin-2, DC immunoreceptor (DCIR), and macrophage-inducible C-type lectin (Mincle) [4, 5, 9, 33, 69]. Notably, expression of some receptors is specific and they can be markers for distinct DC subsets; langerin (CD207) on Langerhans cells (LCs) and blood DC antigen (BDCA)-2 (CD303) on plasmacytoid DCs (pDCs) [25, 99]. Most of the genes for these group II receptors are also clustered in or next to the NKC (Fig. 17.2) [55]. In contrast to KLRs, most receptors of both groups contain fully conserved CRDs binding carbohydrates, and are considered to work as pattern recognition receptors (PRRs) recognizing various pathogen-associated molecular patterns (PAMPs). Especially, dectin-1 is critical for recognition of fungal β-glucan and has a collaborative effect with Toll-like receptor (TLR) 2 on yeast-induced activation signals, whereas DC-SIGN is involved in the recognition of a variety of microorganisms including viruses, bacteria, fungi, and parasites, and suppresses the immune activation signals induced by these pathogens [13, 32, 100]. For these pathogen-recognizing CTL receptors, "CLRs" have been designated analogous to other PRRs, such as TLRs, NOD-like receptors (NLRs), and RIG-I–like receptors (RLRs) [37]. Notably, most of the CLRs are linked to the signaling cascade through the immunoreceptor tyrosine-based activating or inhibitory motif (ITAM or ITIM, respectively), which was first identified in paired KLRs [38, 102]. Hemi-ITAM in dectin-1 and ITAM of Fc receptor γ chain (FcRγ) associated with dectin-2, BDCA-2, and mincle recruit spleen tyrosine kinase (Syk) leading to activating signals,
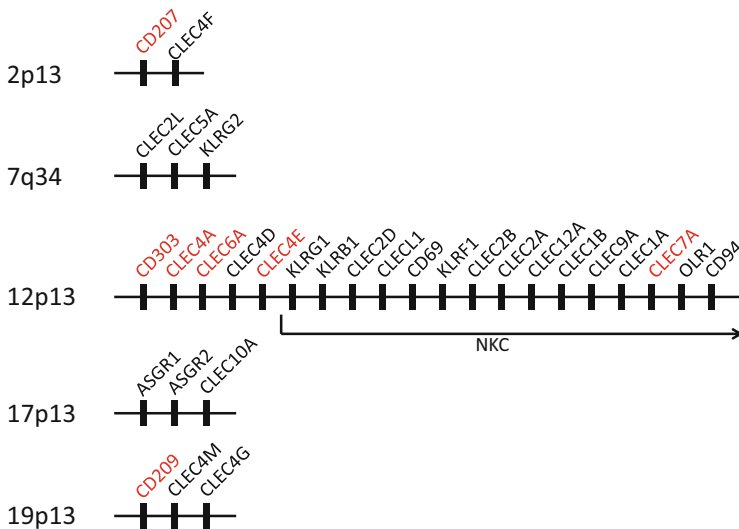
Fig. 17.2 Clustering of CLR genes. Names of the genes for CLRs discussed in this chapter are shown in *red*

whereas ITIM in DCIR recruits Src homology two domain-containing tyrosine phosphatases (SHPs) exhibiting inhibitory effects (Fig. 17.3) [57, 74]. In addition, some of them are also able to bind endogenous self-molecules and are involved in some pathophysiological aspects. For example, DC-SIGN have a role in cellular trafficking, DC-SIGN and dectin-1 can mediate an interaction between DC and T cells, and dectin-2 is involved in ultraviolet (UV)-induced tolerance [2, 5, 33, 35]. Furthermore, dectin-1 and DCIR are involved in the development of autoimmunity in mice, and SNPs in *CLEC4A* and *CLEC4E* encoding DCIR and mincle, respectively, are reportedly associated with autoimmune arthritis [31, 47, 65, 108, 115].

In this chapter, some representative CLRs are picked up and their structural features leading to the functional consequences are discussed, especially on the signaling cascades and pathogen interactions, including some impacts on cutaneous pathophysiology. Regarding the nomenclature, genes for the CLRs have formally been designated by the symbol "CLEC (C-type lectin domain containing)", which is approved by the Human Genome Organization Gene Nomenclature Committee (HGNC) (http://www.genenames.org/genefamilies/CLEC).
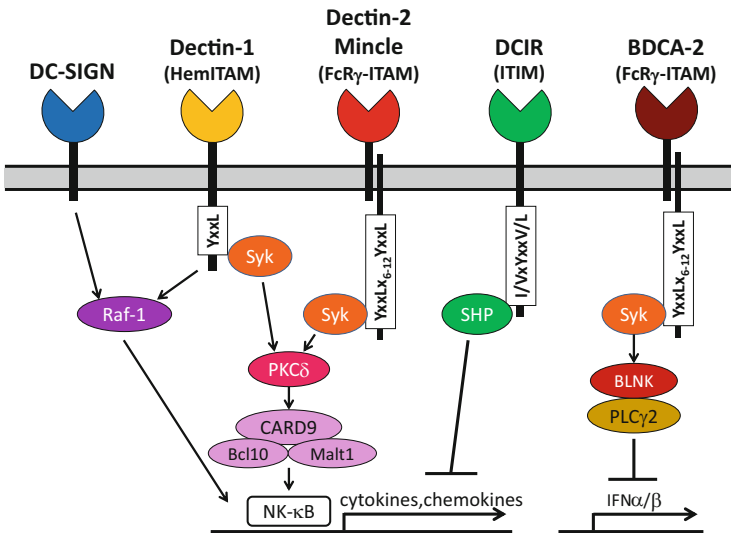
Fig. 17.3 Representative signaling cascades through distinct intracellular motifs of CLRs (HemITAM and ITIM) or ITAM of the associating FcRγ

17.2   Selected CLRs

17.2.1   *Langerin (CD207, CLEC4K)*

Langerhans cells (LCs) are immature DCs resident in the epidermis (see Chap. 4). As sentinels, they form a honeycomb-like network and spread dendrites to the skin surface through epidermal tight junctions. Once they capture and internalize antigens, they modulate expression of adhesion molecules and chemokine receptors to migrate through dermal lymphatics into the draining lymph node and there, after maturation, they present processed antigens to the specific T cells. LCs have been defined electron-microscopically by the presence of Birbeck granules (BGs) with a "tennis-racket"-like appearance, and immunohistochemically with BG-specific Lag antibody [12, 56].

Langerin has been designated as the first surface LC marker recognized by the LC-specific monoclonal antibody (mAb) DCGM4, and subsequently isolated by the expression cloning strategy [98, 99]. Recent structural analysis has revealed that langerin stands as a stable homotrimer via the coiled-coil interaction of its neck region [28]. Langerin has no signaling motif other than the proline-rich domain for internalization in its intracellular domain. However, the presence of such an intracellular domain provides a possibility that langerin interacts with other proteins to modulate or mobilize cellular machanisms required for defense against pathogens, such as interfering viral TLR signaling [100].

As predicted by the presence of EPN (glutamate–proline–asparagine) motif in its CRD, langerin can bind mannose, fucose, and N-acetylglucosamine structures and this binding leads to internalization and transfer of the antigen into BGs, which consist of superimposed and zippered plasma membrane [92, 99]. Langerin deficiency by the W264R point mutation in humans abolished the BG formation without apparent immunodeficiency [103]. Notably, langerin expression is not specific in LCs but is also detected in a part of dermal DCs in mice [14, 39, 75]. By analysis of langerin-DTR mice, in which langerin-expressing cells were transiently depleted by diphteria toxin administration, distinct ontogeny of langerin$^+$ dermal DCs from migrating LCs have been revealed.

Langerin recognizes human immunodeficiency virus (HIV)-1 through high-mannose structures in its envelope glycoprotein gp120 [19]. In contrast to dermal/submucosal DCs, which transmit HIV-1 to T cells through DC-SIGN, epidermal/mucosal LCs clear HIV-1 and prevent its infection to T cells through langerin without inflammation. Immunoelectron-microscopic analysis showed that HIV-1 was captured by langerin and internalized into BGs, to be finally degraded. Therefore, langerin on epidermal LCs is considered a natural barrier to HIV-1 infection. As inhibition of langerin caused HIV-1 infection in LCs and its subsequent transmission to T cells, anti-HIV therapeutics should not interfere with langerin expression or functions.

Langerin also recognizes *Candida* and *Malassezia* species through cell wall mannose structures and β-glucans [18, 96]. *Mycobacterium* species are also

recognized and the langerin binding to their components such as lipoarabino-mannan (LAM) leads to its internalization into BGs and efficient loading to CD1a for presentation to T cells [49]. Therefore, BGs might be an organelle specialized to load glycolipid antigens to CD1a.

17.2.2 DC-SIGN (CD209, CLEC4L)

Although DC-SIGN has been designated by its pivotal role on DC-T cell inter-action, it is well-known as a PRR for a variety of pathogens. Indeed, it was first cloned from placenta as a HIV-1 gp120-binding protein independent of CD4 [17]. DC-SIGN stands as a tetramer and contains dileucine (LL) and YxxL internal-ization motif in its intracellular domain [90]. Its binding to gp120 was inhibited by mannan, D-mannose, and L-fucose and, after binding, gp120 was immediately internalized [17]. DC-SIGN does not allow HIV-1 entry into DCs, but promotes its efficient infection in *trans* of cells expressing CD4 and chemokine receptors [34]. DC-SIGN also functions for capturing dengue virus, a mosquito-mediated flavivirus that causes hemorrhagic fever, and is indispensable for its infection to DCs [73, 95]. Interestingly, the cytoplasmic tail of DC-SIGN is not essential for, but enhances dengue virus infection to DCs. DC-SIGN is also involved in infection of other viruses such as Ebola, cytomegaloviruses, human C-type hepatitis virus (HCV), measles, and severe acute respiratory syndrome (SARS) coronavirus, bacteria such as *Helicobacter pylori* and *Klebsiela Pneumonae*, fungi such as *Candida albicans*, and parasites such as *Leishmania pifanoi* and *Schistosoma mansoni* [74, 101].

DC-SIGN further works for capturing and internalizing *Mycobacterium* species (*M. tuberculosis* and BCG) through the mannose-capped mycobacterial cell wall LAM (ManLAM) [36]. In immature DCs, internalized mycobacteria or ManLAM are transported into lysosome, where they are colocalized with LAMP1. Notably, targeting DC-SIGN with soluble ManLAM inhibits mycobacteria- or lipopoly-saccharide (LPS)-induced DC maturation and induces IL-10 production, suggesting that DC-SIGN signaling interferes with the TLR signaling to cause an anti-inflammatory effect. Such an effect has been shown to be mediated by a serine/threonine kinase Raf1 signaling, which does not require the cytoplasmic YxxL motif of DC-SIGN but involves formation of a distinct protein complex (LSP1, KSR, CNK, LARG, and RhoA) with DC-SIGN [42]. Raf1 signaling does not induce DC activation but modulates TLR-mediated nuclear factor (NF)-κB acti-vation, resulting in increased and prolonged transcription of IL-10 and some other cytokines. By analysis of bronchoalveolar lavage cells, alveolar macrophages from tuberculosis patients specifically expressed DC-SIGN, and its expression was induced by *M. tuberculosis* independently of TLR4, IL-4, and IL-13 [97]. Indeed, accumulation of *M. tuberculosis* in DC-SIGN-expressing alveolar macrophages was immunohistochemically shown.

By the case-control studies, a single nucleotide polymorphism (SNP) in the promoter region of DC-SIGN, −336 C has reportedly been involved in a risk for parenteral HIV-1 infection in European Americans [68]. It has also been reported that −336 SNP is associated with severity of dengue diseases, including severe dengue fever and dengue hemorrhagic fever [86]. In tuberculosis, association of −871 SNP has further been reported by analysis of a South African population living in the areas showing a high incidence rate of tuberculosis [6]. −871G and −336A are associated with protection against tuberculosis, and their combination showed a higher frequency in non-African populations, possibly as a result of genetic adaptation to a longer history of exposure to tuberculosis.

Recently, it has been reported that the anti-inflammatory capacity of intravenous immunoglobulin (Ig) is recapitulated in mice expressing human DC-SIGN, by transfer of bone-marrow–derived macrophages or DCs treated with the Fc fragment of IgG containing glycans terminating in sialic acids (IgG-sFc) [1]. Treatment with IgG-sFc induced IL-33 production in macrophages/DCs and caused expansion of IL-4–producing basophils in their administered mice, which in turn increased expression of an inhibitory Fc receptor, FcγRIIB, on effector macrophages. Such a novel IgG-sFc–induced DC-SIGN–mediated Th2/regulatory pathway might be an endogenous mechanism for immunological homeostasis and provide a line of evidence for therapeutic effects of intravenous Ig administration on various inflammatory diseases such as Kawasaki disease, autoimmune dermatomyositis/vasculitis/neuropathy, myasthenia gravis, pemphigus vulgaris, and severe drug eruptions [88].

17.2.3 Dectin-1 (CLEC7A)

Dectin-1 was originally reported as a DC-specific lectin that had been cloned from a cDNA library of murine XS52 cells after subtraction of J774 macrophage library [5]. At first, dectin-1 was considered a costimulatory molecule because soluble recombinant dectin-1 stimulated T-cell proliferation. However, subsequently, dectin-1 was identified as a β-glucan receptor on macrophages with a different binding site from that for T cells [13]. Dectin-1 is capable of binding a major yeast cell wall component zymosan and a variety of β-glucans from fungi and plants, however, it does not recognize carbohydrates with other linkages. Although the CLEC7A gene is located within the NKC, dectin-1 expression is not observed in NK cells, but in myeloid cells including monocytes, DC, macrophages, and neutrophils [55, 114].

Dectin-1 has a cooperative role with TLR2 on zymosan-induced macrophage activation [32]. Dectin-1 and TLR2 are colocalized on the surface of zymosan-treated macrophages and the zymosan-induced activation signals require dectin-1 as well as TLR2. Notably, the YxxL hemi-ITAM (hemITAM) in the cytoplasmic tail of dectin-1 is shown to be essential for this activation. Upon zymosan-binding, this hemITAM directly recruits and activates spleen tyrosine kinase (Syk), probably

dependent on the receptor dimerization, which induces NF-κB activation through interaction with caspase recruitment domain (CARD) nine coupled with the Bcl10–Malt1 complex [46, 82]. Recently, protein kinase (PK) C-δ was identified to link Syk activation and CARD9 signaling [93]. This Syk activation also induces IL-1β secretion, through pro-IL–1β transcription and processing, mediated by the CARD9-Bcl10–Malt1 and the Malt1-ASC–caspase 8 complex, respectively [45]. The latter complex is called noncanonical caspase 8-dependent inflammasome. Additionally, zymosan-induced dectin-1–dependent signals reportedly include phospholipase (PL) Cγ2-dependent Ca^{2+} influx leading to activation of mitogen-activated protein kinases (MAPKs) as well as NF-κB [109].

Furthermore, NLRP3 inflammasome is activated through dectin-1–Syk signaling in *Mycobacterium abscessus* (Mabc)-activated human macrophages, whereas both TLR2 and dectin-1 are required for Mabc-induced IL-1β secretion [63]. A cytoplasmic scaffold protein p62/SQSTM1 mediates this dectin 1-Syk–NLRP3 pathway, at least partly through production of reactive oxygen species (ROS).

Finally, Raf1 signaling, which regulates NF-κB activation independently of Syk, is also involved in the dectin-1 activation, as observed in case of the DC-SIGN activation [43]. Among Syk-induced cytokines, expressions of IL-1β, IL-6, IL-10, and IL-12 are enhanced but the IL-23 expression is impaired by Raf1 signaling, and, therefore, Th1 responses become dominant by dectin-1 activation. Notably, although both soluble monomer and particulate polymer of β-glucan can bind dectin-1, only the polymer can activate dectin-1 signaling by forming a so-called "phagocytic synapse," by not only clustering the receptor but also excluding inhibitory receptors with tyrosine phosphatase activities, CD45 and CD148 [40].

Interestingly, ZAP70-deficient SKG mice reportedly developed autoimmune arthritis only in the presence of dectin-1 agonist, indicating a role of dectin-1 signaling as a trigger for manifestation of subclinical autoimmune phenotype [115]. Furthermore, zymosan-mediated dectin-1 signaling induced IL-23 production and exacerbated autoimmunity through Th1/Th17 responses in TLR2-deficient mice, whereas zymosan-mediated TLR2 signaling activated Foxp3+ regulatory T (Treg) cells through induction of IL-10 and Raldh2, an essential enzyme in retinoic acid metabolism [66]. Thus, antifungal dectin-1 signaling is considered rather aggressive and regulated by the simultaneous TLR2 signaling to prevent autoimmunity. Notably, dectn-1–deficient mice were shown to be impaired in zymosan recognition and increased in susceptibility to *Candida albicans* infection, whereas, in another report, they were rather more susceptible to *Pneumocystis carini* infection [83, 94].

In 2009, a nonsense mutation (Y238X) in the *CLEC7A* gene was identified in a Dutch family with chronic mucocutaneous candidiasis (OMIM#613108) [29]. The mutation was homozygous in three sisters with vulvovaginal candidiasis and/or onychomycosis and heterozygous in their parents with onychomycosis. The mutated dectin-1, which lacks C-terminal 10 amino acids, showed defective β-glucan binding and induction of cytokine productions after stimulation with β-glucan or *Candida albicans*. However, fungal phagocytosis and killing were shown to be unaffected and, therefore, invasive fungal infection was not observed

in the patients. The allele frequency of the Y238X variant is reportedly 0.069 in the healthy Dutch population and identified carriers are all heterozygous, and the variant has never been found in the Chinese population [29]. In addition, the same variant was reported to be a risk factor of increased susceptibility to invasive aspergillosis in hematopoietic stem cell transplantation, with the highest risk in cases where the variant is present in both donors and recipients [16].

17.2.4   *Dectin-2 (CLEC6A)*

Dectin-2 was reported as another DC-specific lectin that had been isolated by subtraction cloning from murine XS52 cells, whereas its human homologue was originally cloned by the database search of human chromosomal sequences homologous to the exon sequences of murine DC immunoactivating receptor (DCAR) [4, 55]. DCAR was identified as the putative activating partner of DC immunoreceptor (DCIR), and the overall amino acid sequence of murine DCAR is highly homologous (61% identity) to murine dectin-2 [54]. Although the gene for dectin-2 (*CLEC6A*) is clustered with those for DCIR (*CLEC4A*) and murine DCAR (*Clec4b*) and located next to the NKC, dectin-2 expression is observed in various myeloid cells including monocytes, macrophages, neutrophils, and DC subsets such as LCs [55].

Indeed, murine DCAR is the first reported DC/macrophage CLR that associates with an $YxxLx_{6-12}YxxL$ ITAM-bearing adaptor molecule, the γ chain of FcR (FcRγ), whereas the direct human orthologue of DCAR is absent and the functional significance of this molecule is still unknown [57]. Similar to murine DCAR, dectin-2 with a short cytoplasmic domain associates with FcRγ, a type I membrane protein with a short ectodomain that contains ITAM intracellularly and provides a docking site for Syk [85]. Dectin-2 stimulation activates the CARD9-Bcl10–Malt1 pathway through PKCδ and induces various cytokines and chemokines mediated by NF-κB activation [80, 93]. Additionally, dectin-2 signaling activates a MAPKs pathway through PLCγ2, as is the case with dectin-1 [41]. Most importantly, through Malt1-mediated selective c-Rel NF-κB subunit activation, dectin-2, but not dectin-1, signaling leads to Th17 responses [44].

As predicted by the presence of EPN motif in its CRD, dectin-2 binds structures with high mannose [70]. Actually, a number of pathogens including fungi such as *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergilus fumigatus*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Microsporum audouinii*, and *Trichophyton rubrum*, as well as parasites such as *Histoplasma capsulatum* and *Schistosoma mansoni*, and *Mycobacterium tuberculosis* are recognized by dectin-2 [57]. Notably, the yeast and hyphal forms of *Candida albicans* induce different responses through dectin-2 [11, 85]. Most impressively, it has been shown by analyses of dectin-2–deficient mice that dectin-2 is essential for protective Th17 response to intravenous infection with *Candida albicans* [84].

By stimulation of murine bone-marrow–derived DCs with soluble schistosomal egg antigens following pretreatment with TLR ligands, NLRP3-dependent IL-1β secretion was increased through dectin-2-FcRγ-Syk signaling and ROS production [79]. Furthermore, house dust mites are also recognized by dectin-2 and induce eicosanoid production, leading to the Th2 responses [7, 8].

Interestingly, murine dectin-2 is reportedly involved in ultraviolet (UV)-induced immune regulation [2]. Although injection of soluble ectodomain of dectin-2 (sDec2) has no effect on induction of contact hypersensitivity (CHS), it inhibits UV-mediated suppression of CHS and tolerance induction. SDec2-binding CD4^{+} CD25^{+} T cells were shown to produce IL-4, IL-10, and TGFβ upon hapten stimulation and to transfer the UV-induced tolerance.

17.2.5   DCIR (CLEC4A) and DCAR (Clec4b)

DCIR was originally identified as a molecule homologous to hepatic asialoglycoprotein receptors and macrophage lectin, by selecting sequences in DC libraries following the database search of human genomic sequences using the tblastn algorithm [9]. DCIR is unique among known DC/macrophage CLRs because of the presence of I/VxxYxxV/L immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic portion. As the ITIM-related signaling capacity of DCIR, SH2 domain-containing tyrosine phosphatase (SHP)-1 and SHP-2 can be recruited to human DCIR upon stimulation [48, 78]. Furthermore, using murine B cells expressing a chimeric receptor containing a cytoplasmic portion of DCIR and ectodomain of FcγRIIB (DCIR-FcR), coligation of DCIR-FcR and B cell receptor (BCR) showed DCIR-ITIM-dependent inhibitory effects on BCR-mediated calcium influx and tyrosine phosphorylation of cellular proteins [52]. On the other hand, murine DCAR was identified as a molecule whose CRD shows 91% amino acid identity with that of DCIR [53]. DCAR interacts with FcRγ to stand efficiently on the cell surface and ligation of the chimeric DCAR-FcR induced activation signals into its expressing cells dependent on the ITAM in FcRγ. Thus, DCIR and DCAR are equipped as structurally and functionally paired immunoreceptors in mice, although the biological significance of their pairing has been undefined [55].

Among in vitro generated human DC subsets, a higher expression of DCIR was observed in CD14^{+}-derived dermal-type DCs than in CD1a^{+}-derived LC-type DCs [9]. In monocyte-derived DCs (moDCs), its expression did not change during differentiation from monocytes to immature DC, but remarkably decreased after stimulation with LPS or CD40 ligand. Notably, DCIR expression was detected not only in myeloid DCs, but also in monocytes, macrophages, B cells, neutrophils, and plasmacytoid DCs (pDCs) [55, 71]. By reverse transcription (RT)-PCR, the only reliable method to distinguish expression of DCIR and DCAR, DCAR was rather limitedly observed, strongly in spleen and lung and weakly in skin and lymph nodes, whereas DCIR was detected ubiquitously. Both increased during the bone-marrow–derived DC development, but increase of the DCAR expression preceded

that of DCIR [53]. Notably, murine DC-specific mAb 33D1 recognized DCIR2, which can be a specific marker for CD8$^-$ DCs located in the red pulp and marginal zone of the spleen [23].

Despite the presence of an EPS (glutamate–proline–serine residues) motif conserved in DCIR and DCAR, which is postulated to recognize galactose residues [21], their recognizing carbohydrates have not been clarified. Notably, DCIR reportedly participates in capturing HIV-1 and its transmission to CD4$^+$ T cells [60]. HIV-1 captured by surface DCIR is stored as intact virion and replicates de novo intracellularly in infected DCs and, subsequently, is transmitted to CD4$^+$ T cells through induced DCIR expression on them, where HIV-1 replication is enhanced [61, 62]. These processes have been shown to be mediated by the ITIM signaling. Furthermore, DCIR can act as an attachment factor for HCV on pDCs [30]. Notably, the binding of HCV to DCIR on pDCs induced specific inhibition of TLR9-induced IFNα production, in contrast to the case of DCIR activation on DCs by anti-DCIR monoclonal antibody (mAb), which induced specific inhibition of TLR8-induced IL-12 and TNFα production [30, 71, 72].

As predicted by the presence of a tyrosine-based internalization motif overlapping with the ITIM, targeting DCIR on DCs with antigen-conjugated Abs induced clathrin-dependent receptor internalization, its trafficking into lysosomal compartments, and efficient antigen cross-presentation to CD8$^+$ T cells [9, 59]. In contrast, targeting murine DCIR2 induced class II presentation to CD4$^+$ T cells, including stimulation of Foxp3$^+$ Treg cells [23, 112].

The most impressive results on in vivo significance of DCIR have been obtained by analyses of DCIR2-deficient mice. They spontaneously developed sialadenitis and enthesisis and exacerbated collagen-induced arthritis with marked expansion of DCs [31]. Furthermore, in humans, by the case-control study, a SNP in the *CLEC4A* gene was shown to be associated with the susceptibility to anticyclic citrulinated peptide Ab (ACPA)-negative rheumatoid arthritis (RA) [47, 65].

17.2.6   BDCA-2 (CD303, CLEC4C)

Among BDCAs, which were designated for a series of antigens recognized by mAbs raised against human CD4$^+$ lineage$^-$ blood DCs, BDCA-2 is unique by its restricted expression on CD11c$^-$ CD123 (IL-3 receptor)^{bright} pDCs in fresh human blood without expression on immature moDCs or CD34$^+$-derived DCs [24]. Although murine dectin-2 was once proposed as the murine homologue of human BDCA-2, its proper murine orthologue is still undefined and murine DCAR, which lacks a human orthologue, is rather considered closely related to human BDCA-2 on structural and functional aspects [74].

In DC subpopulations, BDCA-2 expression was detected strongly in pDCs and very weakly in immature moDCs, and its expression level was downregulated after culture with IL-3 in pDCs and after maturation with LPS in moDCs [3, 25, 26].

In tonsil, BDCA-2 expression was observed on CD123$^+$ pDCs that were primarily present in T-cell areas but not in the germinal center.

Similar to DCAR and dectin-2, BDCA-2 associates with FcRγ and cross-linking of BDCA-2 on pDCs results in intracellular Ca^{2+} mobilization depending on Src-family protein tyrosine kinases and on tyrosine phosphorylation of cellular proteins [15, 25]. However, unlike other FcRγ-coupled CLRs, BDCA-2 signaling does not lead to NF-κB activation through the Syk–PKCδ–CARD9 pathway, but passes through the Syk–BLNK–PLCγ2 pathway [81]. Indeed, contrary to its predicted immunoactivating property, ligation of BDCA-2 suppressed the production of type I IFN and the secretion of TNF-related apoptosis-inducing ligand (TRAIL) in pDCs induced by various TLR agonists [25, 76]. Furthermore, inhibition of type I IFN production enhances IL-12 production in pDCs to polarize immune responses towards Th1 [26]. BDCA-2-mediated suppression of type I IFN production by CpG oligonucleotides or by influenza virus suggests that viruses target BDCA-2 for immune escape. On the other hand, the same phenomenon induced by antidouble-stranded DNA mAb plus plasmid DNA or by sera from patients of systemic lupus erythematosus (SLE) suggests that targeting BDCA-2 is beneficial for treatment of SLE.

As predicted by the presence of the triglutamate (EEE) late endosomal sorting motif in the cytoplasmic portion of BDCA-2, it was reported that targeting BDCA-2 with mAb induced internalization of the Ab complexes through phosphorylation of actin, tubulin, and clathrin, resulting in antigen presentation to CD4$^+$ T cells [25]. However, more recently, BDCA-2 signaling has rather been shown to inhibit antigen processing and presentation to T cells by pDCs, and, furthermore, to suppress the induction of costimulatory molecules on CpG-stimulated pDCs [51].

Although BDCA-2 contains the EPN motif in its CRD similar to dectin-2, it has recently been reported that BDCA-2 recognizes asialo-galactosyl-oligosaccharides with terminal β-galactose residues and that pDCs bind to subsets of CD14$^+$ monocytes, moDCs, and several tumor cell lines via recognition of asialo-galactosyl-oligosaccharides by BDCA-2 [77]. Accordingly, these cells can introduce the suppression signal into their binding pDCs through BDCA-2, especially on type I IFN secretion. Furthermore, BDCA-2 can bind gp120 of HIV-1 and HCV glycoprotein E2, both of which can also suppress the type I IFN secretion by pDCs [30, 67].

17.2.7   Mincle (CLEC4E)

Mincle was originally identified from murine peritoneal macrophages by subtraction cloning as a molecule specifically induced by activation of NF-IL6 transcription factor [69]. Mincle is expressed on monocytes, macrophages, neutrophils, myeloid DCs, and subsets of B cells, but not on T cells, pDCs, and NK cells [104].

Mincle associates with FcRγ dependently on the positively charged arginine residue in the transmembrane portion of mincle, as is the case with murine DCAR

but is not the case with dectin-2 [110]. Mincle-FcRγ activation induces signaling through Syk–PKCδ–CARD9–NF–κB and MAPK pathways, resulting in the induction of various cytokines and chemokines.

As predicted by the presence of the EPN motif in its CRD, mincle can bind carbohydrates containing α-mannose or other structures, and fungal, mycobacterial, and necrotic cell components have been identified as ligands for mincle [50, 106, 111]. The *Candida albicans* cell wall component was one of the first identified ligands and mincle was shown to mediate the protective antifungal immunity [106]. *Malassezia* is also recognized by mincle and induces cytokine and chemokine production and inflammatory cell recruitment through mincle [111]. Mincle also recognizes *Fonsecaea pedrosoi*, which was revealed to cause chromomycosis in the skin due to insufficient costimulation of TLR on mincle signaling [91].

Mincle also recognizes mycobacterial trehalose dimycolate (TDM), which is an immunomodulatory glycolipid component and has been called mycobacterial cord factor, and mediates TDM or synthetic trehalose dibehenate-induced inflammatory responses including production of cytokines and nitric oxide, NLRP3 inflammasome activation, Th1 and Th17 activation, and granuloma formation [50, 64, 87, 89, 107]. However, in mincle-deficient mice, variable inflammatory responses were observed dependent on the species of infected mycobacteria, probably because they contained different combinations of PAMPs [10, 64]. Interestingly, mycobacteria-induced granuloma formation was unaffected irrespective of mycobacteria species.

Also interesting is that the significance of mincle expression was reportedly different in monocytes and neutrophils. Mincle expression was associated with cytokine production in monocytes, whereas it was rather associated with fungal uptake and killing in neutrophils [104]. Furthermore, the expression of mincle was reciprocally detected between monocytes and neutrophils in individuals.

Mincle also works as a sensor for necrosis by recognizing spliceosome-associated protein (SAP) 130 released from necrotic cells [110]. Notably, mincle has been shown to use a different binding site for SAP130 from that used for carbohydrate recognition. Although it is predictable that mincle is involved in the regulation of autoimmunity, an autoimmune phenotype of mincle-deficient mice has never been reported. In contrast, it has recently been reported that a SNP in the *CLEC4E* gene is associated with ACPA-positive RA [108].

17.3   Concluding Remarks

As described in this chapter, critical roles of the representative CLRs have been revealed in the responses for viral, fungal, and mycobacterial infections, as well as in the maintenance of immunological homeostasis (Table 17.1). As a surface barrier to environmental stimuli including invasive pathogens, skin provides the first battlefield and dermatologists should prepare more and better ways to combat pathogens and keep homeostasis. CLRs should certainly provide targets to develop effective vaccination and therapeutics for distinct infectious and autoimmune/inflammatory diseases.

Table 17.1 Summary of the characteristics of selected CLRs

	CD	CLEC	Tail Motif	Signaling Enzymes	CTD Motif	Interacting Pathogens	Functions
Langerin	CD207	CLEC4K	P-rich	None	EPN	HIV-1 (gp120), *Candida, Malassezia*, Mycobacteria (LAM)	BG formation, HIV-1 degradation, glycolipid antigen loading to CD1a
DC-SIGN	CD209	CLEC4L	LL, YxxL	Raf-1		HIV-1 (gp120), dengue, ebola, CMV, HCV, measles, SARS, *Helicobacter pilori, Klebsiela Pneumonae, Leishmania pifanoi, Schistosoma mansoni, Candida albicans*, Mycobacteria (ManLAM), IgG-sFc	In *trans* HIV-1 infection, interfere with TLR signal for pathogen immune escape (suseptibility to HIV-1 infection and tuberculosis), IVIG anti-inflammatory effect
Dectin-1		CLEC7A	HemITAM	Syk, PLCγ2, Raf-1		*Candida albicans, Pneumocystis carini, Mycobacterium abscessus*	Prevention of mucocutaneous candidiasis, Exacerbation of autoimmunity
Dectin-2		CLEC6A	FcRγ-ITAM	Syk, PLCγ2	EPN	*Candida albicans, Saccharomyces cerevisiae, Aspergillus fumigatus, Cryptococcus neoformans, Paracoccidioides brasiliensis, Microsporum audouinii, Trichophyton rubrum, Histoplasma capsulatum, Schistosoma mansoni, Mycobacterium tuberculosis*, house dust mite, CD4$^+$ CD25$^+$ T cells	Th17 response to *Candida albicans* infection, house dust mite-induced Th2 responses, UV-induced tolerance
DCIR		CLEC4A	ITIM, Y-internalization	SHP-1, SHP-2	EPS	HIV-1, HCV	HIV-1 infection, susceptibility to ACPA-negative RA
BDCA-2	CD303	CLEC4C	FcRγ-ITAM, EEE	Syk	EPN	HIV-1 (gp120), HCV, monocytes, moDCs, tumor cell lines	Suppression of type I IFN production by pDCs
Mincle		CLEC4E	FcRγ-ITAM	Syk	EPN	*Candida albicans, Malassezia, Fonsecaea pedrosoi*, Mycobacteria (cord factor, TDM), necrotic cells (SAP130)	Antifungal and mycobacterial immunity, susceptibility to ACPA-positive RA

References

1. Anthony RM, Kobayashi T, Wermeling F et al (2011) Intravenous gammaglobulin suppresses inflammation through a novel Th2 pathway. Nature 475:110–113
2. Aragane Y, Maeda A, Schwarz A et al (2003) Involvement of dectin-2 in ultraviolet radiation-induced tolerance. J Immunol 171:3801–3807
3. Arce I, Roda-Navarro P, Montoya MC et al (2001) Molecular and genomic characterization of human *DLEC*, a novel member of the C-type lectin receptor gene family preferentially expressed on monocyte-derived dendritic cells. Eur J Immunol 31:2733–2740
4. Ariizumi K, Shen GL, Shikano S et al (2000) Cloning of a second dendritic cell-associated C-type lectin (dectin-2) and its alternatively spliced isoforms. J Biol Chem 275:11957–11963
5. Ariizumi K, Shen GL, Shikano S et al (2000) Identification of a novel, dendritic cell-associated molecule, dectin-1, by subtractive cDNA cloning. J Biol Chem 275:20157–20167
6. Barreiro LB, Neyrolles O, Babb CL et al (2006) Promoter variation in the DC-SIGN-encoding CD209 is associated with tuberculosis. PLoS Med 3:e20
7. Barrett NA, Maekawa A, Rahman OM, Austen KF, Kanaoka Y (2009) Dectin-2 recognition of house dust mite triggers cysteinyl leukotriene generation by dendritic cells. J Immunol 182:1119–1128
8. Barrett NA, Rahman OM, Fernandez JM et al (2011) Dectin-2 mediates Th2 immunity through the generation of cysteinyl leukotrienes. J Exp Med 208:593–604
9. Bates EE, Fournier N, Garcia E et al (1999) APCs express DCIR, a novel C-type lectin surface receptor containing an immunoreceptor tyrosine-based inhibitory motif. J Immunol 163:1973–1983
10. Behler F, Steinwede K, Balboa L et al (2012) Role of mincle in alveolar macrophage-dependent innate immunity against mycobacterial infections in mice. J Immunol 189: 3121–3129
11. Bi L, Gojestani S, Wu W et al (2010) CARD9 mediates dectin-2-induced IκBα kinase ubiquitination leading to activation of NF-κB in response to stimulation by the hyphal form of Candida albicans. J Biol Chem 285:25969–25977
12. Birbeck MS (1962) Electron microscopy of melanocytes. Br Med Bull 18:220–222
13. Brown GD, Gordon S (2001) A new receptor for beta-glucans. Nature 413:36–37
14. Bursch LS, Wang L, Igyarto B et al (2007) Identification of a novel population of Langerin$^+$ dendritic cells. J Exp Med 204:3147–3156
15. Cao W, Zhang L, Rosen DB et al (2007) BDCA2/Fc epsilon RI gamma complex signals through a novel BCR-like pathway in human plasmacytoid dendritic cells. PLoS Biol 5:e248
16. Cunha C, di Ianni M, Bozza S et al (2010) Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanism of antifungal immunity. Blood 116: 5394–5402
17. Curtis BM, Scharnowske S, Watson AJ (1992) Sequence and expression of a membrane-associated C-type lectin that exhibits CD4-independent binding of human immunodeficiency virus envelope glycoprotein gp120. Proc Natl Acad Sci U S A 89:8356–8390
18. de Jong MA, Vriend LE, Theelen B et al (2010) C-type lectin Langerin is a beta-glucan receptor on human Langerhans cells that recognizes opportunistic and pathogenic fungi. Mol Immunol 47:1216–1225
19. de Witte L, Nabatov A, Pion M et al (2007) Langerin is a natural barrier to HIV-1 transmission by Langerhans cells. Nat Med 13:367–371
20. Drickamer K (1988) Two distinct classes of carbohydrate-recognition domains in animal lectins. J Biol Chem 263:9557–9560
21. Drickamer K (1993) Evolution of Ca^{2+}-dependent animal lectins. Prog Nucleic Acid Res 45: 207–232
22. Drickamer K (1999) C-type lectin-like domains. Curr Opin Struct Biol 9:585–590

23. Dudziak D, Kamphorst AO, Heidkamp GF et al (2007) Differential antigen processing by dendritic cell subsets in vivo. Science 315:107–111
24. Dzionek A, Fuchs A, Schmidt P et al (2000) BDCA-2, BDCA-3, and BDCA-4: three markers for distinct subsets of dendritic cells in human peripheral blood. J Immunol 165:6037–6046
25. Dzionek A, Sohma Y, Nagafune J et al (2001) BDCA-2, a novel plasmacytoid dendritic cell-specific type II C-type lectin, mediates antigen capture and is a potent inhibitor of interferon α/β induction. J Exp Med 194:1823–1834
26. Dzionek A, Inagaki Y, Okawa K et al (2002) Plasmacytoid dendritic cells: from specific surface markers to specific cellular functions. Hum Immunol 63:1133–1148
27. East L, Isacke CL (2002) The mannose receptor family. Biochem Biophys Acta 1572: 364–386
28. Feinberg H, Powlesland AS, Taylor ME et al (2010) Trimeric structure of langerin. J Biol Chem 285:13285–13293
29. Ferwerda B, Ferwerda G, Plantinga TS et al (2009) Human dectin-1 deficiency and muco-cutaneous fungal infections. N Engl J Med 361:1760–1767
30. Florentin J, Aouar B, Dental C et al (2012) HCV glycoprotein E2 is a novel BDCA-2 ligand and acts as in inhibitor of IFN production by plasmacytoid dendritic cells. Blood 120: 4544–4551
31. Fujikado N, Saijo S, Yonezawa T et al (2008) Dcir deficiency causes development of autoimmune diseases in mice due to excess expansion of dendritic cells. Nat Med 14:176–180
32. Gantner BN, Simmons RM, Canavera SJ et al (2003) Collaborative induction of inflammatory responses by dectin-1 and toll-like receptor 2. J Exp Med 197:1107–1117
33. Geijtenbeek TB, Torensma R, van Vliet SJ et al (2000) Identification of DC-SIGN, a novel dendritic cell-specific ICAM-3 receptor that supports primary immune responses. Cell 100: 575–585
34. Geijtenbeek TB, Kwon DS, Torensma R et al (2000) DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. Cell 100:587–597
35. Geijtenbeek TB, Krooshoop DJ, Bleijs DA et al (2000) DC-SIGN-ICAM-2 interaction mediates dendritic cell trafficking. Nat Immunol 1:353–357
36. Geijtenbeek TB, van Vliet SJ, Koppel EA et al (2003) Mycobacteria target DC-SIGN to suppress dendritic cell function. J Exp Med 197:7–17
37. Geijtenbeek TB, van Vliet SJ, Engering A et al (2004) Sef- and nonself-recognition by C-type lectins on dendritic cells. Annu Rev Immunol 22:33–54
38. Gergely J, Pecht I, Sarmay G (1999) Immunoreceptor tyrosine-based inhibition motif-bearing receptors regulate the immunoreceptor tyrosine-based activation motif-induced activation of immune competent cells. Immunol Lett 68:3–15
39. Ginhoux F, Collin MP, Bogunovic M et al (2007) Blood-derived dermal langerin+ dendritic cells survey the skin in the steady state. J Exp Med 204:3133–3146
40. Goodridge HS, Reyes CN, Becker CA et al (2011) Activation of the innate immune receptor dectin-1 upon formation of a 'phagocytic synapse'. Nature 472:471–475
41. Gorjestani S, Yu M, Tang B et al (2011) Phospholipase Cγ2 (PLCγ2) is key component in dectin-2 signaling pathway, mediating anti-fungal innate immune responses. J Biol Chem 286:43651–43659
42. Gringhuis SI, den Dunnen J, Litjens M et al (2007) C-type lectin DC-SIGN modulates toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. Immunity 26:605–616
43. Gringhuis SI, den Dunnen J, Litjens M et al (2009) Dectin-1 directs T helper cell differen-tiation by controlling noncanonical NF-κB activation through Raf-1 and Syk. Nat Immunol 10:203–213
44. Gringhuis SI, Wevers BA, Kaptein TM et al (2011) Selective c-Rel activation via Malt1 controls anti-fungal T(H)-17 immunity by dectin-1 and dectin-2. PLoS Pathog 7:e1001259

45. Gringhuis SI, Kaptein TM, Wevers BA et al (2012) Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1-beta via a noncanonical caspase-8-inflammasome. Nat Immunol 13:246–254

46. Gross O, Gewies A, Finger K et al (2006) Card9 controls a non-TLR signaling pathway for innate anti-fungal immunity. Nature 442:651–656

47. Guo J, Wu X, Too CL et al (2012) A replication study confirms the association of dendritic cell immunoreceptor (DCIR) polymorphisms with ACPA-negative RA in a large Asian cohort. PLoS One 7:e41228

48. Huang X, Yuan Z, Chen G et al (2001) Cloning and characterization of a novel ITIM containing lectin-like immunoreceptor LLIR and its two transmembrane region deletion variants. Biochem Biophys Res Commun 281:131–140

49. Hunger RE, Sieling PA, Ochoa MT et al (2004) Langerhans cells utilizes CD1a and langerin to efficiently present nonpeptide antigens to T cells. J Clin Invest 113:701–708

50. Ishikawa E, Ishikawa T, Morita YS et al (2009) Direct recognition of the mycobacterial glycolipid, trehalose dimycolate, by C-type lectin Mincle. J Exp Med 206:2879–2888

51. Jahn PS, Zanker KS, Schmitz J et al (2010) BDCA-2 signaling inhibits TLR9-agonist-induced plasmacytoid dendritic cell activation and antigen presentation. Cell Immunol 265:15–22

52. Kanazawa N, Okazaki T, Nishimura H et al (2002) DCIR acts as an inhibitory receptor depending on its immunoreceptor tyrosine-based inhibitory motif. J Invest Dermatol 118:261–266

53. Kanazawa N, Tashiro K, Inaba K et al (2003) Dendritic cell immunoactivating receptor, a novel C-type lectin immunoreceptor, acts as an activating receptor through association with Fc receptor γ chain. J Biol Chem 278:32645–32652

54. Kanazawa N, Tashiro K, Inaba K et al (2004) Molecular cloning of human dectin-2. J Invest Dermatol 122:1522–1524

55. Kanazawa N (2007) Dendritic cell immunoreceptors: C-type lectin receptors for pattern recognition and signaling on antigen-presenting cells. J Dermatol Sci 45:77–86

56. Kashihara-Sawami M, Horiguchi Y, Ikai K et al (1988) Letterer-Siwe disease: immunopathologic study with a new monoclonal antibody. J Am Acad Dermatol 18:646–654

57. Kerscher B, Willment JA, Brown GD (2013) The dectin-2 family of C-type lectin-like receptors: an update. Int Immunol 25:271–277

58. Kilpatrick DC (2002) Animal lectins: a historical introduction and overview. Biochim Biophys Acta 1572:187–197

59. Klechevsky E, Flamar AL, Cao Y et al (2010) Cross-priming CD8^{+} T cells by targeting antigens to human dendritic cells through DCIR. Blood 116:1685–1697

60. Lambert AA, Gilbert C, Richard M et al (2008) The C-type lectin surface receptor DCIR acts as a new attachment factor for HIV-1 in dendritic cells and contributes to trans- and cis-infection pathways. Blood 112:1299–1307

61. Lambert AA, Imbeault M, Gilbert C et al (2010) HIV-1 induces DCIR expression in CD4^{+} T cells. PLoS Pathog 6:e1001188

62. Lambert AA, Barabe F, Gilbert C et al (2011) DCIR-mediated enhancement of HIV-1 infection requires the ITIM-associated signal transduction pathway. Blood 117:6589–6599

63. Lee HM, Yuk JM, Kim KH et al (2012) Mycobacterium abscessus activates the NLRP3 inflammasome via dectin-1-Syk and p62/SQSTM1. Immunol Cell Biol 90:601–610

64. Lee WB, Kang JS, Yan JJ et al (2012) Neutrophils promote mycobacterial trehalose dimycolate-induced lung inflammation via the Mincle pathway. PLoS Pathog 8:e1002614

65. Lorentzen JC, Flornes L, Eklow C et al (2007) Association of arthritis with a gene complex encoding C-type lectin-like receptors. Arthritis Rheum 56:2620–2632

66. Manicassamy S, Ravindran R, Deng J et al (2009) Toll-like receptor 2-dependent induction of vitamin a-metabolizing enzymes in dendritic cells promotes T regulatory responses and inhibits autoimmunity. Nat Med 15:401–409

67. Martinelli E, Cicala C, Van Ryk D et al (2007) HIV-1 go120 inhibits TLR9-mediated activation and IFN-α secretion in plasmacytoid dendritic cells. Proc Natl Acad Sci U S A 104:3396–3401

68. Martin MP, Lederman MM, Hutcheson HB et al (2004) Association of DC-SIGN promoter polymorphism with increased risk for parenteral, but not mucosal, acquisition of human immunodeficiency virus type 1 infection. J Virol 78:14053–14056

69. Matsumoto M, Tanaka T, Kaisho T et al (1999) A novel LPS-inducible C-type lectin is a transcriptional target of NF-IL6 in macrophages. J Immunol 163:5039–5048

70. McGreal EP, Rosas M, Brown GD et al (2006) The carbohydrate-recognition domain of dectin-2 is a C-type lectin with specificity for high mannose. Glycobiology 16:422–430

71. Meyer-Wentrup F, Benitez-Ribas D, Tacken PJ et al (2008) Targeting DCIR on human plasmacytoid dendritic cells results in antigen presentation and inhibits IFN-alpha production. Blood 111:4245–4253

72. Meyer-Wentrup F, Cambi A, Joosten B et al (2009) DCIR is endocytosed into human dendritic cells and inhibits TLR8-mediated cytokine production. J Leukoc Biol 85:518–525

73. Navarro-Sanchez E, Altmeyer R, Amara A et al (2003) Dendritic-cell-specific ICAM3-grabbing non-integrin is essential for the productive infectionof human dendritic cells by mosquito-cell-derived dengue viruses. EMBO Rep 4:723–728

74. Osorio F, Reis e Sousa C (2011) Myeloid C-type lectin receptors in pathogen recognition and host defense. Immunity 34:651–664

75. Poulin LF, Henri S, de Bovis B, Davilard E, Kissenpfennig A, Malissen B (2007) The dermis contains langerin^{+} dendritic cells that develop and function independently of epidermal Langerhans cells. J Exp Med 204:3119–3131

76. Riboldi E, Daniele R, Cassatella MA et al (2009) Engagement of BDCA-2 blocks TRAIL-mediated cytotoxic activity of plasmacytoid dendritic cells. Immunobiology 214:868

77. Riboldi E, Daniele R, Parola C et al (2011) Human C-type lectin domain family 4, member C (CLEC4C/BDCA-2/CD303) is a receptor for asialo-galactosyl-oligosaccharides. J Biol Chem 286:35329–35333

78. Richard M, Thibault N, Veilleux P et al (2006) Granulocyte macrophage-colony stimulating factor reduces the affinity of SHP-2 for the ITIM of CLECSF6 in neutrophils: a new mechanism of action for SHP-2. Mol Immunol 43:1716–1721

79. Ritter M, Gross O, Kays S et al (2010) *Schistosoma mansoni* triggers dectin-2, which activates the Nlrp3 inflammasome and alters adaptive immune responses. Proc Natl Acad Sci U S A 107:20459–20464

80. Robinson MJ, Osorio F, Rosas M et al (2009) Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. J Exp Med 206:2037–2051

81. Rock J, Schneider E, Grun JR et al (2007) CD303 (BDCA-2) signals in plasmacytoid dendritic cells via a BCR-like signalosome involving Syk, Slp65 and PLCγ2. Eur J Immunol 37:3564–3575

82. Rogers NC, Slack EC, Edwards AD et al (2005) Syk-dependent cytokine induction by dectin-1 reveals a novel pattern recognition pathway for C type lectins. Immunity 22:507–517

83. Saijo S, Fujikado N, Furuta T et al (2007) Dectin-1 is required for host defense against pneumocystis carinii but not against Candida albicans. Nat Immunol 8:39–46

84. Saijo S, Ikeda S, Yamabe K et al (2010) Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation is essential for host defense against *Candida albicans*. Immunity 32:681–691

85. Sato K, Yang XL, Yudate T et al (2006) Dectin-2 is a pattern recognition receptor for fungi that couples with the Fc receptor gamma chain to induce innate immune responses. J Biol Chem 281:38854–38866

86. Sakuntabhai A, Turbpaiboon C, Casademont I et al (2005) A variant in the CD209 promoter is associated with severity of dengue disease. Nat Genet 37:507–513

87. Schoenen H, Bodendorfer B, Hitchens K et al (2010) Mincle is essential for recognition and adjuvanticity of the mycobacterial cord factor and its synthetic analog trehalose-dibehenate. J Immunol 184:2756–2760

88. Schwab I, Nimmerjahn F (2013) Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol 13:176–189

89. Schweneker K, Gorka O, Schweneker M et al (2012) The mycobacterial cord factor adjuvant analogue trehalose-6,6′-dibehenate (TDB) activates the Nlrp3 inflammasome. Immunobiology 218:664–673

90. Soilleux EJ, Barten R, Trowsdale J (2000) DC-SIGN; a related gene, DC-SIGNR; and CD23 form a cluster on 19p13. J Immunol 165:2937–2942

91. Sousa Mda G, Reid DM, Schweighoffer E et al (2011) Restoration of pattern recognition receptor costimulation to treat chromoblastomycosis, a chronic fungal infection of the skin. Cell Host Microbe 9:436–443

92. Stambach NS, Taylor ME (2003) Characterization of carbohydrate recognition by langerin, a C-type lectin of Langerhans cells. Glycobiology 13:401–410

93. Strasser D, Neumann K, Bergmann H et al (2012) Syk kinase-coupled C-type lectin receptors engage protein kinase C-δ to elicit Card9 adaptor-mediated innate immunity. Immunity 36:32–42

94. Taylor PR, Tsoni SV, Wilment JA et al (2007) Dectin-1 is required for beta-glucan recognition and control of fungal infection. Nat Immunol 8:31–38

95. Tassaneetrithep B, Burgess TH, Granelli-Piperno A et al (2003) DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. J Exp Med 197:823–829

96. Tateno H, Ohnishi K, Yabe R et al (2010) Dual specificity of Langerin to sulfated and mannosylated glycans via a single C-type carbohydrate recognition domain. J Biol Chem 285:6390–6400

97. Tailleux L, Schwartz O, Herrmann JL et al (2003) DC-SIGN is the major mycobacterium tuberculosis receptor on human dendritic cells. J Exp Med 197:121–127

98. Valladeau J, Duvert-Frances V, Pin JJ et al (1999) The monoclonal antibody DCGM4 recognizes Langerin, a protein specific of Langerhans cells, and is rapidly internalized from the cell surface. Eur J Immunol 29:2695–2704

99. Valladeau J, Ravel O, Dezutter-Dambuyant C et al (2000) Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. Immunity 12:71–81

100. van der Vlist M, Geijtenbeek TB (2010) Langerin functions as an antiviral receptor on Langerhans cells. Immunol Cell Biol 88:410–415

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

102. Vely F, Vivier E (1997) Conservation of structural features reveals the existence of a large family of inhibitory cell surface receptors and noninhibitory/activatory counterparts. J Immunol 159:2075–2077

103. Verdijk P, Dijkman R, Plasmeijer EI et al (2005) A lack of Birbeck granules in Langerhans cells is associated with a naturally occurring point mutation in the human Langerin gene. J Invest Dermatol 124:714–717

104. Vijayan D, Radford KJ, Beckhouse AG et al (2012) Mincle polarizes human monocyte and neutrophi responses to Candida albicans. Immunol Cell Biol 90:889–895

105. Weis WI, Taylor ME, Drickamer K (1998) The C-type lectin superfamily in the immune system. Immunol Rev 163:19–34

106. Wells CA, Salvage-Jones JA, Li X et al (2008) The macrophage-inducible C-type lectin, mincle, is an essential component of the innate immune response to Candida albicans. J Immunol 180:7404–7413

107. Werninghaus K, Babiak A, Gross O et al (2009) Adjuvanticity of a synthetic cord factor analogue for subunit *Mycobacterium tuberculosis* vaccination requires FcRgamma-Syk-Card9-dependent innate immune activation. J Exp Med 206:89–97

108. Wu XY, Guo JP, Yin FR et al (2012) Macrophage-inducible C-type lectin is associated with anti-cyclic citrullinated peptide antibodies-positive rheumatoid arthritis in men. Chin Med J 125:3115–3119
109. Xu S, Huo J, Lee KG et al (2009) Phospholipase Cγ2 is critical for dectin-1-mediated Ca^{2+} flux and cytokine production in dendritic cells. J Biol Chem 284:7038–7046
110. Yamasaki S, Ishikawa E, Sakuma M et al (2008) Mincle is an ITAM-coupled activating receptor that senses damaged cells. Nat Immunol 9:1179–1188
111. Yamasaki S, Matsumoto M, Takeuchi O et al (2009) C-type lectin mincle is an activating receptor for pathogenic fungus, *Malassezia*. Proc Natl Acad Sci U S A 106: 1897–1902
112. Yamazaki S, Dudziak D, Heidkamp GF et al (2008) CD8^{+} CD205^{+} splenic dendritic cells are specialized to induce Foxp3^{+} regulatory T cells. J Immunol 181:6923–6933
113. Yokoyama WM, Plougastel BF (2003) Immune functions encoded by the natural killer gene complex. Nat Rev Immunol 3:304–316
114. Yokota K, Takashima A, Bergstresser PR et al (2001) Identification of a human homologue of the dendritic cell-associated C-type lectin-1, dectin-1. Gene 272:51–60
115. Yoshitomi H, Sakaguchi N, Kobayashi K et al (2005) A role for fungal beta-glucans and their receptor dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. J Exp Med 201:949–960
116. Zelensky AN, Gready JE (2005) The C-type lectin-like domain superfamily. FEBS J 272:6179–6217