C-Type Lectin Receptors in Host Defense Against Microbial Pathogens

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Rikio Yabe, Yoichiro Iwakura, and Shinobu Saijo

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R. Yabe (✉)
Center for Animal Disease Models, Research Institute for Biomedical Science, Tokyo University of Science, Noda, Chiba, Japan

Division of Molecular Immunology, Medical Mycology Research Center, Chiba University, Chiba, Japan
e-mail: rikio-yabe@rs.tus.ac.jp; walatte@yahoo.co.jp

Y. Iwakura
Center for Animal Disease Models, Research Institute for Biomedical Science, Tokyo University of Science, Noda, Chiba, Japan

Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency (JST), Saitama, Japan
e-mail: iwakura@rs.tus.ac.jp

S. Saijo
Division of Molecular Immunology, Medical Mycology Research Center, Chiba University, Chiba, Japan

Precursory Research for Embryonic Science and Technology (PRESTO), JST, Saitama, Japan
e-mail: saijo@faculty.chiba-u.jp

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Abstract

C-type lectin receptors (CLRs) are a group of pattern recognition receptors (PRRs) that recognize carbohydrate structures in microbes, including fungi and bacteria, as pathogen-associated molecular patterns (PAMPs). They are expressed mainly in dendritic cells (DCs) and macrophages, and among these CLRs, DC-associated C-type lectin-1 (Dectin-1), DC-associated C-type lectin-2 (Dectin-2), macrophage-inducible C-type lectin (Mincle), and macrophage C-type lectin (Mcl) transduce their signaling through phosphorylation of spleen tyrosine kinase (Syk). On the other hand, human DC-specific intracellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) and its mouse homologue SIGN-related gene 3 (SIGNR3), members of the DC-SIGN superfamily of CLRs, transduce their signaling through intracellular tyrosine-containing motif. In addition to pathogen recognition, Mincle, DC-SIGN, and SIGNR3 have been shown to recognize molecules from self, suggesting pleiotropic roles of CLRs in the homeostasis of the body. Here, we review each of these receptors in detail describing their expression, ligand recognition, signaling, and associated human diseases.

Keywords

C-type lectin receptor • Pathogen • Innate immunity • Cytokine • Th17 • Dectin-1 • Dectin-2 • Mincle • Mcl • DC-SIGN • Carbohydrate

Introduction

Innate immune responses are important for the host defense against microbial infection. Invading pathogens are first recognized by antigen-presenting cells (APCs) such as DCs and macrophages through PRRs. CLRs, glycoproteins mainly expressed in DCs and macrophages, are one of such PRRs. A group of CLRs recognizes carbohydrate structures termed PAMPs on the cell walls of bacteria, fungi, and parasites in a Ca^{2+}-dependent manner through a carbohydrate recognition domain (CRD) in the extracellular carboxy-terminal part and plays important roles for the protection against these pathogens. One of the CLRs, Dectin-1 (gene symbol: *Clec7a*), contains immunoreceptor tyrosine-based activation motif (ITAM)-like motif in the cytoplasmic portion. Many of CLRs, however, such as Dectin-2 (gene symbol: *Clec4n*), Mincle (gene symbol: *Clec4e*), and Mcl (gene symbol: *Clec4d*), do not have any signaling motif in their cytoplasmic domains and, instead, recruit the ITAM-containing adaptor molecule Fc receptor γ chain (FcRγ, gene symbol: *Fcer1g*) to transduce signals (Fig. 1). *Clec4n*, *Clec4d*, *Clec4e*, and *Clec7a* are mapped in the close vicinity on the mouse chromosome 6 (Balch et al. 2002). Upon recognition of their ligands, CLRs form dimers or tetramers and recruit phosphorylated Syk (Fig. 2). Then, phosphorylated Syk activates a CARD9-BCL10-MALT1 (CBM) complex, followed by nuclear factor of κ light polypeptide gene enhancer in B-cells 1 (NF-κB) activation. NF-κB activation induces expression of inflammatory cytokines such as interleukin-23 (IL-23) and

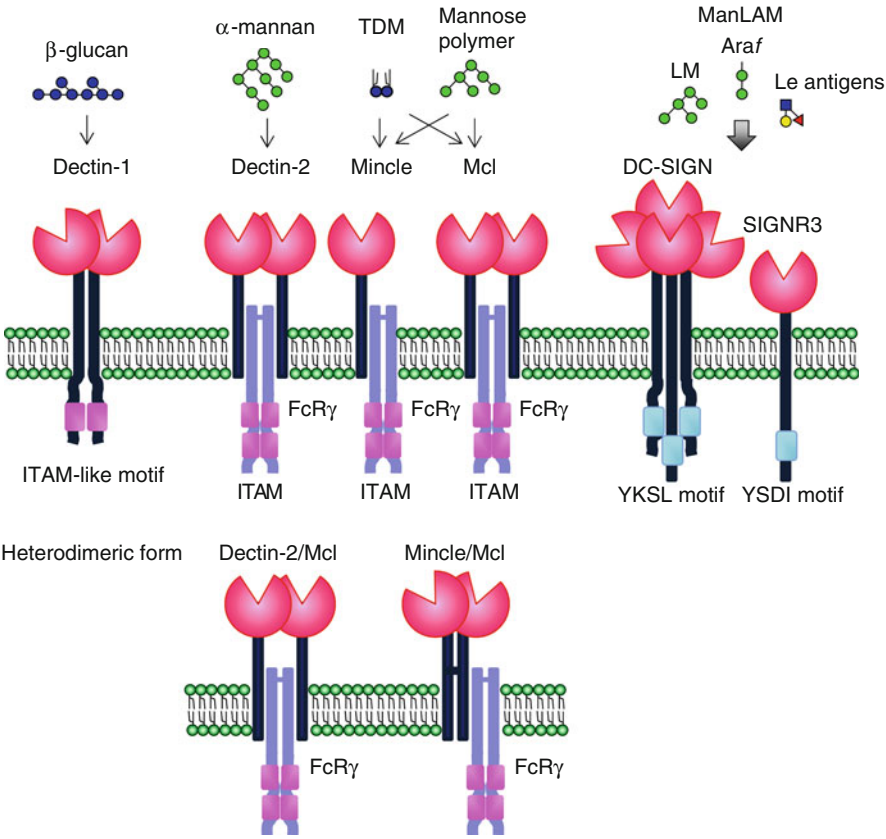

Fig. 1 CLRs and their ligands. Dectin-1 contains an ITAM-like motif in its cytoplasmic region, while Dectin-2, Mincle, and Mcl associate with FcRγ, which contains ITAM. DC-SIGN and SIGNR3 contain their own signaling motifs in their cytoplasmic domains. Dectin-1 is present as a monomer and forms homodimer upon ligand binding. Dectin-2 and Mcl form homodimer associated with FcRγ. Mcl forms heterodimer with Mincle linked by a disulfide bond, while Mcl forms heterodimer with Dectin-2 through FcRγ association. DC-SIGN forms a homo-tetrameric architecture

pro-IL-1β. At the same time, Syk activation induces reactive oxygen species (ROS) production. ROS is important for the direct killing of pathogens and activation of inflammasome that enhances processing of pro-IL-1β into mature IL-1β. The mitogen-activated protein kinase (MAPK) pathway is also activated simultaneously, although the biological significance of this pathway in the host defense mechanism is not known (Saijo and Iwakura 2011) (Fig. 2).

On the other hand, DC-SIGN (gene symbol: *Cd209a*) is another CLR that consists of a transmembrane domain with a stalk and a CRD capable of recognizing carbohydrate structures on pathogens. *Cd209a* is mapped to chromosome 8 together with 7 related genes (Park et al. 2001; Powlesland et al. 2006). DC-SIGN has no

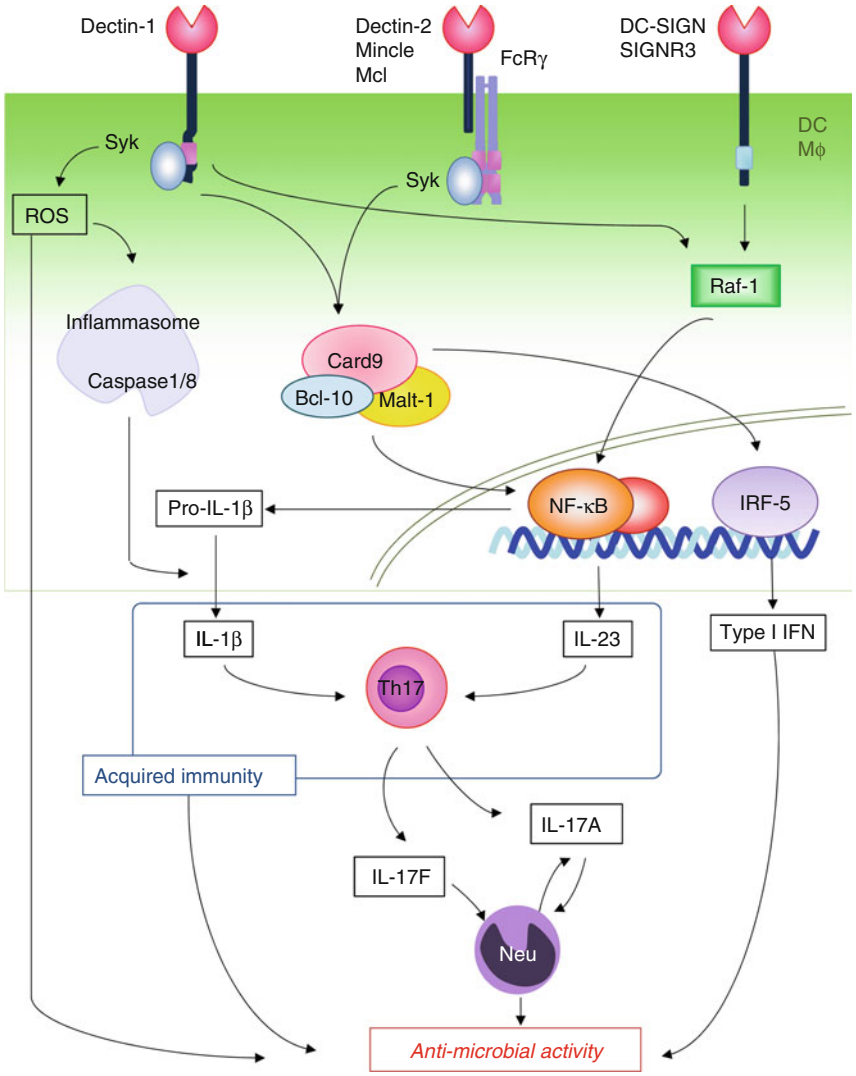

Fig. 2 Upon β-glucan binding, Dectin-1 recruits Syk to its ITAM-like motif, following the activation of the CBM complex. ROS production is induced in a Syk-dependent manner, resulting in fungal killing and activation of inflammasome. Raf-1 is activated in a Syk-independent manner. Similar to Dectin-1, upon α-mannan binding to Dectin-2, Syk is recruited to the ITAM of the FcRγ chain. TDM binding to Mcl and Mincle also activate the CBM complex through activation of Syk. In response to *C. albicans*, Dectin-1 and Dectin-2, but not Mincle, signaling induce type I IFN production in a Syk-CARD9-IRF5-dependent manner. Human DC-SIGN and its murine homologue SIGNR-3 bind to ManLAM, following the activation of Raf-1. The CBM complex as well as Raf-1 activates NF-κB, resulting in the induction of cytokines such as pro-IL-1β and IL-23. Activation of inflammasome activates Caspase 1 and/or Caspase 8 to process pro-IL-1β into mature IL-1β. IL-1β and IL-23 preferentially induce differentiation of Th17 cells that plays an important role in the host defense against fungal infection by recruiting neutrophils

ITAM or does not associate with FcRγ chain. Instead, human DC-SIGN and the mouse homologue SIGN-related gene 3 (SIGNR3, gene symbol: *Cd209d*) have YKSL and YSDI motifs, respectively, in their cytoplasmic regions that mediate intracellular signaling events through activation of the serine/threonine kinase Raf1 in APCs, causing cytokine production. This family of CLR plays an important role for the defense against pathogens as a PRR. In this review, we will introduce the roles of these CLRs, which are mainly expressed in APCs to activate antimicrobial immunity.

Dectin-1

Dectin-1 has an ITAM-like motif in its intracellular region (Fig. 1), which is conserved in mice and humans. By using an expression-cloning strategy, Dectin-1 was suggested to be a β-glucan receptor (Brown and Gordon 2001).

β-glucans are an important cell-wall component of fungi; the backbone structure consists of polymerized β-1,3-linked β-D-glucopyranosyl units with β-1,6-linked side chains. Purified β-glucans strongly induce proinflammatory cytokines including tumor necrosis factor (TNF), IL-6, and IL-1β as well as ROS in vitro, and it was shown that Dectin-1 is the sole functional receptor for β-glucans on DCs by generating Dectin-1-deficient mice (Fig. 2) (Saijo et al. 2007; Taylor et al. 2007). Dectin-1-deficient mice are more susceptible to fungi, e.g., *Pneumocystis carinii* and *Candida albicans* (*C. albicans*). People with Dectin-1 gene mutations develop chronic mucocutaneous candidiasis, suggesting the requirement of Dectin-1 in the host defense against fungi. However, the importance of Dectin-1 may vary depending on the virulence of the pathogens. It is widely accepted that the β-glucan layer is buried between the mannan and chitin layers as a skeletal component of yeast form candida cell walls, but β-glucans are exposed on the cell surface at budding sites. Interestingly, Dectin-1 requirement in the control of systemic *C. albicans* infection is specific to fungal strains, and the levels of cell-wall chitin influence the strain-specific Dectin-1 dependency of *C. albicans* eradication (Marakalala et al. 2013).

Recently, it was reported that Dectin-1 or its homologue Dectin-2 (see below) mediates interferon-β (IFN-β) production during *C. albicans* recognition (del Fresno et al. 2013). The IFN-β production requires Syk and the transcriptional factor interferon regulatory factor 5 (IRF5), but not IRF3 and IRF7. By using type I IFN receptor-deficient mice, it was found that IFN-β production plays a crucial role in the host defense against the fungal infection.

Dectin-1 also plays an important role in the maintenance of the intestinal microflora (Iliev et al. 2012). A rich fungal community is found in the mammalian gut with the interaction between the host immune system through Dectin-1 in a certain environment. In this context, the polymorphism in the gene for CARD9 in humans, an adaptor molecule in the downstream of Dectin-1, is strongly associated with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, suggesting CLRs are important for intestinal homeostasis in humans.

Dectin-2

Dectin-2 has an EPN motif, a Ca^{2+}-dependent mannose-binding amino acid sequence, in its extracellular CRD. It has no known signaling motif in the cytoplasmic domain, but associates with FcRγ chain, which contains ITAM (Fig. 1). A study using glycan array reveals that Dectin-2 binds to high-mannose structures that are distributed in a wide range of species including fungi, parasites, bacteria, and mammals (Table 1). *C. albicans* has α-1,2-linked mannose residues attached to α-1,6-linked mannose backbone that contains high-mannose-type *N*-glycan structures in the cell wall. Because mannosyl residues locate in the outermost layer of the *C. albicans* cell wall, it is considered that mannose recognition should be the first step for the host to activate innate immune system. As expected, Dectin-2-deficient mice show higher susceptibility to *C. albicans* infection (Saijo et al. 2010; Robinson et al. 2009). The importance of Dectin-2 in the antifungal immunity is shown not only in *C. albicans* but also in *C. glabrata* and *Aspergillus fumigatus* (*A. fumigatus*).

Deficient mice for IL-17A and IL-23-p19 are more susceptible to *C. albicans* infection, suggesting that IL-17A is important for the host protection (Saijo et al. 2010; Kagami et al. 2010). Furthermore, inborn errors in human IL-17F and IL-17 receptor A (IL-17RA) cause impaired IL-17 immunity, resulting in the development of chronic mucoepithelial fungal infection (Puel et al. 2011). Consistent with these observations, both Dectin-1- and Dectin-2-induced cytokines preferentially promote Th17 cell differentiation in vitro. However, it still remains to elucidate the IL-17A and IL-17F producer cells upon infection with fungi. Regarding this, it was reported that IL-17F is produced by epithelial cells and innate immune cells other than Th17 cells (Ishigame et al. 2009). Moreover, it was recently reported that upon infection with *A. fumigatus*, Dectin-2-, but not Dectin-1-, induced IL-6 and IL-23 induce IL-17A production in neutrophils that constitutively express the transcription factor retinoid-related orphan receptor gamma t (RORγt). IL-6 and IL-23 also induce expression of IL-17RC and Dectin-2 in an autocrine manner, resulting in the production of ROS and increased fungal killing (Taylor et al. 2014) (Fig. 2).

Dectin-2 also senses mannan-containing parasites including house dust mite and *Schistosoma mansoni* (*S. mansoni*). In these cases, Dectin-2 seems to induce Th1, Th2, as well as Th17 differentiation, suggesting a broader swath of the immunological roles.

Mincle

Mincle is expressed in macrophages and can be induced by the stimulation with inflammatory cytokines and Toll-like receptor ligands (TLRLs). Like Dectin-2, Mincle is an FcRγ-coupled activating receptor containing an EPN motif in its CRD (Fig. 1). Consistent with this, glycan array analysis demonstrates that Mincle binds to polyvalent α-mannose. Mincle directly senses manno-glycoconjugates on fungi

Table 1 CLRs sensing microbial pathogens

Name	Microbial pathogens	Ligands
Dectin-1	*C. albicans*	β-glucans
	P. carinii	
	Leishmania infantum	
	Coccidioides posadasii	
	Histoplasma capsulatum	
	Mycobacterium spp.	
Dectin-2	*C. albicans*	High-mannose-type *N*-glycans
	C. glabrata	α-mannans
	S. mansoni	*O*-linked mannobioses
	Malassezia spp.	
	A. fumigatus	
	Coccidioides spp.	
	Blastomyces dermatitidis	
	Histoplasma capsulatum	
	M. tuberculosis	
	House dust mite	
Mincle	*C. albicans*	Highly mannosylated glycans
	Malassezia pachydermatis	Mannosyl fatty acids
	M. tuberculosis	TDM
Mcl	*C. albicans*	α-mannans
	M. bovis	TDM
	K. pneumonia	
DC-SIGN	*M. tuberculosis*	Highly mannosylated glycans
	Helicobacter pylori	ManLAM
	S. mansoni	Lewis$^{a/b/x/y}$
	Lactobacillus spp.	
SIGNR3	*Leishmania infantum*	Man-terminated glycans
	S. mansoni	Fuc-terminated glycans
		GlcNAc-terminated glycans

such as *Saccharomyces cerevisiae*, *C. albicans*, and *Malassezia* species (Table 1), mediating the induction of proinflammatory cytokines such as IL-6 and TNF, although this receptor does not mediate phagocytosis of *C. albicans*. Mincle-deficient mice show higher susceptibility to systemic *C. albicans* infection than WT mice (Wells et al. 2008), and cytokine production and neutrophil infiltration are suppressed upon infection with *Malassezia* (Yamasaki et al. 2009), indicating that Mincle is an important activating receptor for host defense against fungi. Furthermore, Mincle is suggested to be involved in the antimycobacterial immunity. Mincle directly senses *Mycobacterium smegmatis* (*M. smegmatis*), *M. bovis*, and *M. tuberculosis*. Mycobacteria species contain unique cell-wall components such as trehalose-6,6′-dimycolate (TDM; also called cord factor), which is a potent immunostimulatory component of the host immune system. Mincle directly recognizes the TDM and provokes massive proinflammatory cytokine secretion and

granuloma formation in the lung (Ishikawa et al. 2009; Schoenen et al. 2010). However, the in vivo roles of Mincle in mycobacterial protection are still controversial; Mincle-deficient mice show no apparent defects during *M. tuberculosis* H37Rv infection, whereas they succumb rapidly after *M. bovis* bacillus Calmette-Guerin (BCG) or *M. tuberculosis* Erdman infections (Schoenen et al. 2010; Lee et al. 2012; Heitmann et al. 2013). This is probably because different mycobacterial strains contain distinct exterior cell-wall components, which are essential for their survival and pathogenicity. Notably, TDM and its analog, treharose-6,6-dibehenate (TDB)-induced macrophage activation and Th1/Th17 cell development are diminished in Mincle-deficient mice, suggesting that Mincle contributes to both innate and adaptive immunity for the protection against mycobacterial infection (Schoenen et al. 2010).

Mcl

Mcl is another FcRγ-coupled activating CLR expressed in myeloid cells. This molecule is unique, however, because it lacks typical positive-charged amino acid residues in its transmembrane domain to associate with FcRγ (Fig. 1). The CRD of Mcl is also atypical, because it lacks conserved triplet-motif essential for Ca^{2+}-dependent carbohydrate recognition. Mcl has a similar ligand spectrum as Mincle in pathogen recognition and recognizes PAMPs with high-mannose type and TDM (Table 1). The Mcl-mediated carbohydrate recognition induces phagocytosis of pathogens, NF-κB activation, and proinflammatory cytokine production in macrophages. Mcl-deficient mice are more sensitive to systemic *C. albicans* infection than WT mice (Zhu et al. 2013) and develop milder inflammation upon immunization with TDM (Miyake et al. 2013). Mcl-deficient mice are also highly susceptible to *Klebsiella pneumonia* infection and die from septic shock (Steichen et al. 2013). It is noteworthy that Mcl forms a heterodimeric complex with Dectin-2 through FcRγ ligation in macrophages under physiological conditions (Fig. 1). Moreover, Mcl forms a complex with Mincle in the presence of FcRγ and drives Mincle expression in DCs upon stimulation. Cooperative signaling by Mcl and Dectin-2, and Mcl and Mincle, may synergistically augment immune responses against pathogens to protect from microbial infection.

DC-SIGN

DC-SIGN recognizes high-mannose-type structures, fucose-containing Lewis antigens, and terminal GlcNAc-containing glycans in the cell wall of microorganisms (Fig. 1; Table 1) and is mainly expressed on DCs. Activation of DC-SIGN on APCs evokes a wide variety of cellular responses such as DC maturation, ligand uptake by endocytosis and/or phagocytosis, and cytokine production. In humans, two superfamily members, *CD209* and its homologue *CD209L* genes, encode DC-SIGN (also known as CD209) and DC-SIGNR (L-SIGN/CD209L), respectively, whereas,

in mice, *DC-SIGN*/*Cd209a* (encoding SIGNR5) and seven closely related genes are identified [*Cd209b* (SIGNR1), *Cd209c* (SIGNR2), *Cd209d* (SIGNR3), *Cd209e* (SIGNR4), *Cd209-ps* (putative SIGNR6, no transcript), *Cd209g* (SIGNR7), and *Cd209f* (SIGNR8)] (Park et al. 2001; Powlesland et al. 2006). From genetic organization of their human/mouse DC-SIGN loci and the phylogenetic tree reconstruction based on amino acid sequences, murine SIGNR3 (*Cd209d*) is identified as the closest functional homologue of human DC-SIGN (Tanne et al. 2009). SIGNR3 also has similar ligand-binding specificity with human DC-SIGN and dual carbohydrate-binding specificity for terminal mannose and fucose moieties. SIGNR3 interacts with the mycobacterial components mannosylated lipoarabinomannan (ManLAM) and lipomannan (LM), and SIGNR3-deficient mice are more sensitive to *M. tuberculosis* infection especially in the early phase probably due to impaired cytokine production (Tanne et al. 2009). In contrast, transgenic mice expressing human DC-SIGN under the control of the CD11c promoter are more resistant against *M. tuberculosis* infection (Schaefer et al. 2008). Collectively, studies using mouse models suggest that DC-SIGN plays an important role in the host defense against *M. tuberculosis* infection in humans. Although SIGNR1, the earlier reported human DC-SIGN homologue, also binds to ManLAM and LM, SIGNR1-deficient mice show normal sensitivity to *M. tuberculosis* infection.

Concluding Remarks

The roles of CLRs in the host defense against pathogen infection have been elucidated with many family members as described in this review. However, functions and in vivo roles of many CLR genes, such as *Dcar1*, *Dcar2*, *Clec12b*, and *Clec1a*, of the same gene cluster, still remain to be elucidated. These studies should bring us important cues to develop novel therapeutics for the treatment of infections. It is also interesting that some of CLRs can recognize multiple ligands. For example, Dectin-2 can recognize *Malassezia O*-linked mannobiose-rich glycoprotein and house dust mite antigens other than α-mannans in fungal cell walls, although the exact structure of the mite antigens has not been known yet. On the other hand, some CLRs exert redundant biological functions in infectious immune responses. For example, Mincle and Mcl recognize similar carbohydrate structures, and DC-SIGN and SIGNRs also recognize similar structures. These convergence and divergence of the function are one of the interesting characteristics of the CLR system, suggesting that the CLR system develops elegantly to respond to all the pathogens in the most powerful way using limited number of CLRs and provide a fail-safe mechanism at the same time. Furthermore, some CLRs can recognize other (s) than PAMPs. For example, Mincle can recognize antigens from SAP130, a component of small nuclear ribonucleoprotein, as danger-associated molecular patterns (DAMPs), suggesting that Mincle may play some physiological roles under normal conditions beyond the roles in host defense mechanism. Thus, elucidating the roles of these CLRs in the homeostasis of the immune system under physiological conditions may be one of most interesting fields in the future.

Lastly, collaboration between CLRs or between CLR and other innate immune receptors, such as TLRs, retinoic acid-inducible gene-I-like receptors (RLRs), or nucleotide oligomerization domain-like receptors (NLRs), is another interesting research field. For instance, CLRs and TLRs collaboratively enhance IL-12 production to induce Th1 differentiation, which is important for fungal and bacterial protection (Gerosa et al. 2008; Dennehy et al. 2009). These studies should bring us the whole picture of the CLR system and their roles in the host defense mechanism that is important for the development of new therapeutics and vaccines.

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