Chapter 1
Dectin-2 in Antimicrobial Immunity and Homeostasis

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Abstract Dendritic cell-associated lectin-2 (Dectin-2) is one of the most well-characterized members of the C-type lectin family. Recent studies have revealed its indispensable functions as a pattern recognition receptor (PRR) for a wide variety of pathogens, including fungi, bacteria, and viruses. This receptor recognizes microbial carbohydrates as a pathogen-associated molecular pattern (PAMP). Upon ligand ligation, Dectin-2 induces secretion of the pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and TNF, as well as the inhibitory cytokine IL-10. These cytokines differentiate T cells into IL-17-producing Th17 cells to eliminate pathogens. In addition to microbes, Dectin-2 also binds to allergens such as those of house dust mites and helminths to activate the NLRP3 inflammasome. In vivo, Dectin-2 plays a key role in antimicrobial infection, especially antifungal infections. Owing to these abilities, Dectin-2 agonists could be promising adjuvants in vaccinations. In this section, we summarize the current knowledge of Dectin-2 in detail, describing its structure, ligand recognition, signaling, and associated human diseases.

Keywords Dectin-2 • Fungal infection • Bacterial infection • Innate immunity • Inflammation • Carbohydrate • High mannose

1.1 Introduction

Dendritic cell-associated lectin-2 (Dectin-2, gene symbol: *Mus musculus Clec4n*, *Homo sapiens CLEC6A* or *CLEC4N*) was originally found as a Langerhans cell-specific C-type lectin that recognizes self-ligands expressed in $CD4^+CD25^+$ T cells (Ariizumi et al. 2000). Subsequently, Dectin-2 expression was found in myeloid cells, including monocytes, tissue macrophages, neutrophils, several dendritic cell (DC) subsets, and B lymphoid cells (McDonald et al. 2012; Robinson et al. 2009; Seeds et al. 2009; Taylor et al. 2005). The expression of the gene is rather low in

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these cells, although it is greatly enhanced with the inflammatory stimuli. Nevertheless, the molecular mechanisms underlying the regulation of Dectin-2 expression still remain to be elucidated.

Dectin-2 is encoded in the mouse chromosome 6F and in the syntenic region on human chromosome 12q13, where several C-type lectin genes are located and form clusters, including Dectin-1 and Dectin-2 clusters (Fig. 1.1a) (Balch et al. 2002; Fujikado et al. 2006). In the mouse, nine members, DCIR4, DCIR3, DCIR2, DCAR2, DCIR1, DCAR-1, Dectin-2, MCL, and Mincle (gene symbols: *Clec4a1*, *Clec4a3*, *Clec4a4*, *Clec4b1*, *Clec4a2*, *Clec4b2*, *Clec4n*, *Clec4d*, and *Clec4e*), are mapped in close vicinity on the Dectin-2 cluster of chromosome 6, sharing a common structure (see next section). By contrast, fewer molecules are found in the Dectin-2 cluster in humans, i.e., BDCA-2, DCIR, DECTIN-2, MCL, and MINCLE (gene symbols: *CLEC4C*, *CLEC4A*, *CLEC6A*, *CLECSF8*, and

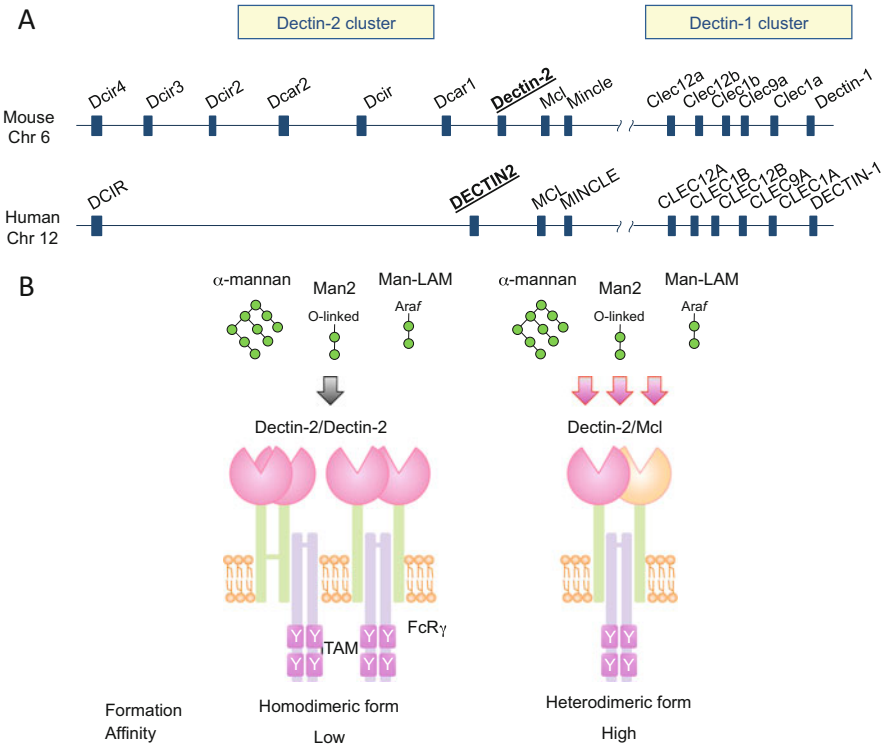

Fig. 1.1 **a** Organization of mouse and human Dectin-1 and Dectin-2 clusters. **b** Dectin-2 senses α-mannosylated chains and initiates cellular responses through association with the Fc receptor γ chain (FcRγ), which contains immunoreceptor tyrosine-based activation motif (ITAMs). Dectin-2 is presented as a homodimer through a disulfide bond or in association with FcRγ, whereas it forms a heterodimer with MCL linked by FcRγ. The heterodimeric complex has relatively strong affinity to pathogen-associated molecular patterns (PAMPs) in comparison with the homodimeric complex

CLEC4E). Due to the common gene structure shared by the receptors and the variation of the family members between species, it is speculated that this gene cluster may have been established by gene duplication. Interestingly, this region of the chromosome harboring the Dectin-2 and Dectin-1 clusters has been implicated in several autoimmune diseases by linkage studies (Fujikado et al. 2006; Wandstrat and Wakeland 2001). Therefore, it is possible that C-type lectins could be one of the susceptibility genes for these diseases (Caliz et al. 2013).

Of note, Dectin-2 may have an immune inhibition role because of its unique ability to produce anti-inflammatory cytokine, interleukin (IL)-10. However, compared to its immune-activating or antimicrobial functions, the physiological role of the immune-inhibiting activity of Dectin-2 remains largely unknown. In this section, we update paradigm and summary findings on Dectin-2 and its functions that have been made in recent years.

1.2 Structure of Dectin-2

Dectin-2 is a glycosylated type II transmembrane protein, whose C-terminal portion encodes the extracellular region and the N-terminal portion encodes the cytoplasmic region of the receptor (Ariizumi et al. 2000). This protein is encoded by six exons and has a single carbohydrate recognition domain (CRD) in the extracellular region, a stalk region, a transmembrane region, and a short cytoplasmic domain with no known signaling motif. These structures are shared among other C-type lectins in the Dectin-2 cluster with the exception of DCIR and DCIR2, which have an inhibitory motif, immunoreceptor tyrosine-based inhibitory motif (ITIM), in their cytoplasmic region. Dectin-2 associates with an adapter molecule, Fc receptor γ chain (FcRγ, gene symbol: *Fcer1g*) to transduce its signaling. Although Dectin-2 contains an arginine residue, which often mediates associations with immunoreceptor tyrosine-based activation motif (ITAM)-containing adaptor molecules in the transmembrane region, the interaction between these two molecules is not dependent on the arginine residue unlike other FcRγ-coupled receptors, but instead requires the cytoplasmic tail of Dectin-2 (Sato et al. 2006). As Dectin-2 has a conserved cysteine residue in its stalk region, which can form disulfide-linked homodimers, it was implicated that this receptor forms homodimers by ligand recognition. Recently, Zhu et al. demonstrated that Dectin-2 forms heterodimers with another C-type lectin, MCL, as well as homodimers, and the heterodimers showed stronger affinity to the ligand than the homodimers (Fig. 1.1b). Requirement of the cysteine residue of Dectin-2 for the heterodimerization and the molecular mechanism for this dimer formation are still unknown.

1.3 Ligands of Dectin-2

Dectin-2 contains an acid–proline–asparagine (EPN) amino acid triplet in its extracellular CRD, a common feature that is known to facilitate binding to mannose, glucose/*N*-acetylglucosamine, and fucose in a Ca^{2+}-dependent manner and has attracted much attention with respect to its role as a pattern recognition receptor (PRR) (Fernandes et al. 1999). Indeed, a study using a glycan array revealed that Dectin-2 binds to high-mannose structures that are distributed in a wide range of species, including fungi, parasites, bacteria, and mammals (McGreal et al. 2006). Consistent with this, using a recombinant soluble form of Dectin-2 CRD as a probe, or Dectin-2-expressing reporter cells, it was shown that Dectin-2 binds to a variety of pathogenic microorganisms, including *Candida* spp., *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, *Trichophyton rubrum*, *Paracoccidioides brasiliensis*, *Malassezia* spp., and *Aspergillus fumigatus*, *Mycobacterium* spp., *Streptococcus pneumoniae*, and *Ebola* virus, whose cell wall polysaccharides contain a high-mannose structure (Table 1.1) (Barrett et al. 2009; Brudner et al. 2013; McGreal et al. 2006; Miyasaka et al. 2013; Ritter et al. 2010; Sato et al. 2006).

Among these pathogens, the best-studied interactions are with *Candida albicans* (*C. albicans*), *Malassezia*, and *Mycobacterium*. The *C. albicans* cell wall is composed of multiple layers, including the outermost mannans (polymers of mannose), middle-layer β-glucans (polymers of D-glucose linked by β-glycosidic bonds), and the inner-layer chitins (polymers of *N*-acetylglucosamine) (Odds 1988). Mannans from *C. albicans* have β-1,2-linked mannose residues attached to their α-1,2-linked oligomannose side chains with α-1,6-linked mannose backbone (Fig. 1.2a) (Cutler 2001; Shibata et al. 2003). Since the β-1,2-linked mannose residues are not synthesized when this fungus is cultured in a carbon-limited (C-limited), low-pH

Table 1.1 Dectin-2 sensing microbial pathogens

Category	Microbial pathogens	Ligands
Bacteria	*Mycobacterium* spp.	Man-LAM
	S. pneumonia	
Fungi	*Candida* spp.	α-mannans, high-mannose-type *N*-glycans
	Malassezia spp.	*O*-linked mannobioses
	A. fumigates	
	C. neoformans (non-capsulated)	
	Saccharomyces cerevisiae	
	Coccidioides spp.	
	B. dermatitidis	
	H. capsulatum	
	T. rubrum	
	P. brasiliensis	
Virus	Ebola	
Others	*S. mansoni*	
	House dust mite allergen	

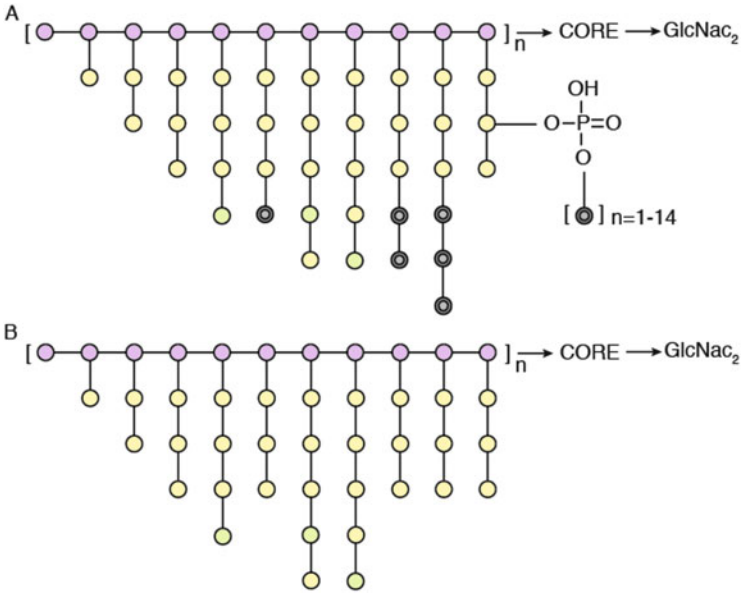

Fig. 1.2 The structure of the mannosyl residues of an *N*-linked mannoprotein. **a** *C. albicans* cultured at 37 °C with normal medium. **b** *C. albicans* cultured at 27 °C with C-limiting medium. α-1,6-linked mannose (*pink circles*), α-1,2-linked mannose (*yellow circles*), β-1,2-linked mannose (*gray circles*), α-1,3-linked mannose (*green*) (Adapted from Hobson et al. 2004)

medium at a low temperature, only α-1,2-mannose residues are synthesized and secreted into the medium as a water-soluble fraction (Shinohara et al. 2006) (Fig. 1.2b). When Dectin-2-deficient bone marrow-derived DCs (BMDCs) are stimulated with these α-mannans, the production of cytokines such as interleukin (IL)-6 and TNF was abolished, indicating that Dectin-2 is a receptor for *C. albicans* α-mannans. *C. albicans* is a dimorphic fungus that can exist in yeast or hyphal form depending on its growth environment (Saijo et al. 2010). A previous study revealed that Dectin-2 selectively binds to the hyphal form of *C. albicans* (Sato et al. 2006). Indeed, significant, but not complete, reduction in cytokine secretion was found in Dectin-2-deficient BMDCs upon stimulation with the hyphal form of *C. albicans*. Notably, cytokine production of Dectin-2-deficient BMDCs was eradicated in response to the yeast form of *C. albicans*, indicating that Dectin-2 is the only receptor to produce cytokines for the yeast form of the fungus.

Malassezia, which is found in the normal flora of the human skin, is another opportunistic fungal pathogen. Ishikawa et al. identified the *O*-linked mannoprotein fractionated from the *Malassezia* cell wall as a distinct Dectin-2 ligand. By using Dectin-2-expressing reporter cells, they also showed that α-1,2-mannosyl residues were necessary and sufficient for recognition by the receptor (Table 1.1) (Ishikawa et al. 2013). Recently, Dectin-2 was found to recognize a cell wall component of *Mycobacterium*, mannose-capped lipoarabinomannan (Man-LAM), which consists of a mannosyl-phosphatidyl-myo-inositol anchor, a mannose backbone, and an

arabinan domain with mannose capping (Yonekawa et al. 2014). Interestingly, a distinct mycobacterial cell wall component, trehalose-6,6′-dimycolate (TDM), is recognized by MINCLE and MCL, whose genes are closely located to the Dectin-2 locus (Ishikawa et al. 2009; Miyake et al. 2013).

1.4 Dectin-2 Signaling

Upon recognition of the carbohydrate structures in pathogens, Dectin-2 initiates a series of cellular responses beginning with the association of the ITAM-containing adaptor molecule FcRγ, followed by recruitment of phosphorylated Syk (Fig. 1.3). Subsequently, phosphorylated Syk activates a CARD9–BCL10–MALT1 (CBM) complex, resulting in activation of nuclear factor (NF)-κB (Hara et al. 2007; Saijo et al. 2010). The activated NF-κB induces expression of inflammatory cytokines such as IL-23 and pro-IL-1β. At the same time, Syk activation induces reactive oxygen species (ROS) production. ROS are important for the direct killing of pathogens and activation of the NLRP3 inflammasome that enhances processing of pro-IL-1β into mature IL-1β (Ritter et al. 2010). 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 (Fig. 1.3).

It is noteworthy that Dectin-2 signaling also induces the production of an inhibitory cytokine, IL-10, by the stimulation of α-mannans of the *C. albicans* cell wall as well as Man-LAM of the *Mycobacterium tuberculosis* cell wall (Saijo et al. 2010; Yonekawa et al. 2014). Since the capping moieties at the terminal extremity of the arabinan domain in LAM differ among *Mycobacterium* species, Man-LAM is rather unique to pathogenic mycobacteria such as *M. tuberculosis*. In this context, it has been shown that *M. tuberculosis* suppresses the host immune system and phagosome–lysosome fusion, suggesting that IL-10 production via the Man-LAM–Dectin-2 interaction might be an explanation for the severe pathogenicity of *M. tuberculosis*.

1.5 Role of Dectin-2 in Diseases

The importance of Dectin-2 in antifungal immunity has been clearly shown in mouse models (Robinson et al. 2009). Dectin-2-deficient mice showed decreased survival against *C. albicans* infection, because of increased fungal growth in the kidney (Saijo et al. 2010). This demonstrated the important role of Dectin-2 in pathogen elimination; however, the in vivo mechanism remains unclear. One possibility is that the pro-inflammatory cytokines secreted from Dectin-2-expressing myeloid cells enhance IL-17 expression in lymphocytes. Indeed, IL-17A-deficient and IL-23-p19-deficient mice are more vulnerable to *C. albicans* infection, suggesting that IL-17A is crucial for the host protection

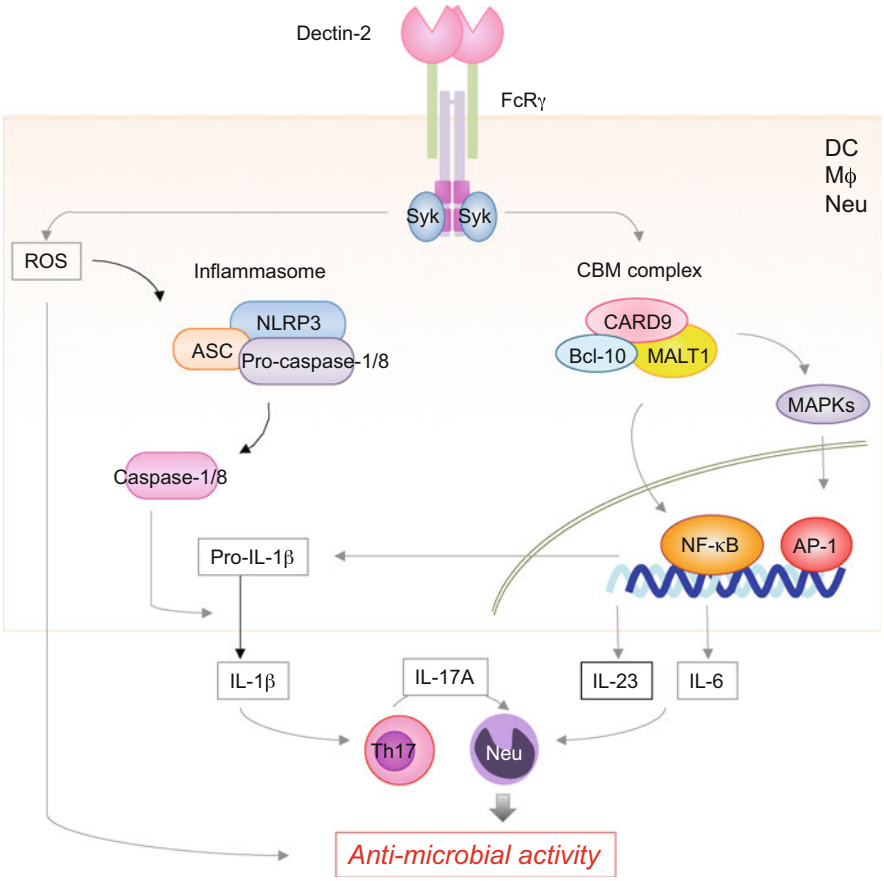

Fig. 1.3 Upon ligand binding, Dectin-2 recruits phosphorylated Syk to ITAM of the FcRγ, leading to activation of the CARD9–BCL10–MALT1 (CBM) complex. At the same time, reactive oxygen species (ROS) production is induced in a Syk-dependent manner, resulting in the direct killing of pathogens and activation of the NLRP3 inflammasome. The CBM complex activates NF-κB, which induces the production of cytokines such as pro-IL-1β, IL-6, and IL-23. In contrast, the NLRP3 inflammasome activates caspase 1 and/or caspase 8 to process pro-IL-1β into mature IL-1β. IL-1β, IL-6, and IL-23 preferentially induce the differentiation of Th17 cells, which play an important role in the host defense against microbes by recruiting neutrophils

against this fungus (Kagami et al. 2010; Saijo et al. 2010). Although single nucleotide polymorphisms (SNPs) or inborn errors in the human Dectin-2 gene have not been reported yet, mutations that affect human IL-17F and IL-17 receptor A (IL-17RA) functions cause the development of chronic mucoepithelial fungal infection (CMC), which is due to impaired IL-17-mediated immunity (Puel et al. 2011). Consistent with these observations, Dectin-2-induced cytokines preferentially promote the differentiation of Th17 cells in vitro, although the specific IL-17A- and IL-17F-producing cells upon fungal infection remain to be elucidated.

On the other hand, it was recently reported that Dectin-2-induced IL-6 and IL-23 enhanced IL-17A production in neutrophils that constitutively express the transcription factor RORγt, upon infection with *A. fumigatus*. IL-6 and IL-23 also induce the 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. 1.3).

Regarding Th17 differentiation caused by Dectin-2-mediated signaling, as described above, Dectin-2 recognizes *Mycobacterium* Man-LAM, which has been known to have both inhibitory and stimulatory effects on host immunity (Briken et al. 2004; Chan et al. 2001; Gringhuis et al. 2009; Mazurek et al. 2012). Man-LAM stimulation of BMDCs cocultured with T cells led to increased production of IL-17 in T cells. More importantly, Man-LAM stimulation was sufficient to promote host immunity for the development of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. Given that Th17 cells play a pivotal role in the pathogenesis in these mice, this *Mycobacterium* component or other Dectin-2 agonists might serve as a beneficial adjuvant (Yonekawa et al. 2014).

Dectin-2 also senses mannan-containing parasites, including house dust mite and *Schistosoma mansoni* (Barrett et al. 2011; Norimoto et al. 2014; Ritter et al. 2010). In these cases, Dectin-2 seems to induce Th1, Th2, as well as Th17 differentiation, suggesting a broader swath of its immunological roles.

1.6 Concluding Remarks

The significant functions of Dectin-2 in the host defense against pathogen infection have been studied and are described in this review. However, the in vivo roles of Dectin-2 remain to be unveiled. Interestingly, some other C-type lectins have redundant biological functions to Dectin-2. For example, MCL senses the same ligand, *C. albicans* α-mannan, as Dectin-2, and, more importantly, MCL and Dectin-2 form heterodimers as well as homodimers (Zhu et al. 2013). On the other hand, MCL also stabilizes Mincle expression, and both receptors sense mycobacterial TDM (Miyake et al. 2013, 2015). These findings suggest that the C-type lectin system provides a sophisticated and fail-safe method to respond to pathogens using a limited number of molecules. Determining the collaboration between C-type lectins and other innate immune receptors such as toll-like receptors (TLRs), retinoic acid-inducible gene-I-like receptors (RLRs), or nucleotide oligomerization domain-like receptors (NLRs) could be another interesting area of research. For instance, Dectin-1 and TLR-2 collaboratively enhance IL-12 production to induce Th1 differentiation, which is important for fungal and bacterial protection (Dennehy et al. 2009; Gerosa et al. 2008). These studies could help to elucidate the whole picture of the role of the C-type lectin system in host defense, with valuable implications for the development of new therapeutic and vaccine strategies.

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