Chapter 4
Dectin-1 (CLEC7A, BGR, CLECSF12)

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Abstract Dectin-1 is the archetypical example of the C-type lectin receptor (CLR) family of pattern recognition receptors (PRRs). Expressed primarily by cells of the innate immune system, this receptor is best known for its role in antifungal immunity through its ability to recognise cell wall β-glucans. Upon recognition of these carbohydrates, Dectin-1 transduces intracellular signalling through several pathways activating or regulating numerous cellular responses such as phagocytosis, the respiratory burst, neutrophil extracellular trap formation, inflammasome activation and cytokine and chemokine production. Moreover, like the Toll-like receptors (TLRs), Dectin-1 is able to instruct the development of adaptive immunity, promoting Th1- and Th17-type responses. Dectin-1 collaborates with other PRRs to synergise and regulate innate and adaptive immune responses. More recently, Dectin-1 has been found to recognise a broader range of microbial pathogens, including bacteria, as well as endogenous ligands, influencing autoimmune and other diseases, including rheumatoid arthritis, ulcerative colitis and cancer. In this chapter, we will discuss the structure, expression and ligands of Dectin-1, as well as the intracellular signalling pathways and cellular responses that this receptor can induce. We will describe the role of Dectin-1 in antifungal immunity and in immunity to other pathogens. We will briefly discuss the interaction of Dectin-1 with other PRRs and its broader role in immunity, through recognition of endogenous ligands, for example.

Keywords Dectin-1 • C-type lectin • ITAM-like • Antifungal immunity • Beta-glucan

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4.1 Dectin-1 Structure, Expression and Ligands

Dectin-1 is a member of the group V C-type lectin family and encoded within the Dectin-1 gene cluster located in the natural gene complex (NKC) on chromosome 6 in mouse and chromosome 12 in human (Zelensky and Gready 2005). This type II transmembrane receptor has a single carbohydrate recognition domain (CRD), a stalk region, a transmembrane region and a cytoplasmic tail (Fig. 4.1a) (Drummond and Brown 2011). The N-terminal cytoplasmic tail has an immunoreceptor tyrosine-based activation motif (ITAM)-like, YXXL, which can activate downstream signalling pathways (Drummond and Brown 2011). The extracellular domains of Dectin-1 possess several putative N- and O-glycosylation sites, and N-glycosylation has been shown to be involved in cell surface expression and function of this receptor (Kato et al. 2006). Dectin-1 is alternatively spliced into two major isoforms (isoforms A and B, the latter of which lacks the stalk region) and several minor isoforms (isoform C–H) (Willment et al. 2001; Heinsbroek et al. 2006). Only the two major isoforms (A and B; Fig. 4.1a) are able to interact with extracellular ligands (Willment et al. 2001; Heinsbroek et al. 2006). Dectin-1 minor isoform E, which contains the CRD and ITAM-like domain, has been shown to be located in the cytoplasm and interact with a Ran binding protein, RanBPM, although the functional significance of this interaction is unclear (Xie et al. 2006).

Dectin-1 is primarily expressed by innate immune cells including neutrophils, monocytes, macrophages and dendritic cells (DCs) (Drummond and Brown 2011). This receptor is also expressed on microglia, eosinophils, mast cells and certain lymphocytes, including B cells and γδ T-cells (Drummond and Brown 2011). On myeloid cells, the expression of this receptor can be regulated by cytokines and growth factors. For example, expression of Dectin-1 is upregulated by granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4 and IL-13, but downregulated by IL-10, LPS and dexamethasone (Willment et al. 2003). There is evidence that expression of Dectin-1 can be induced on epithelial cells (Lee et al. 2009; Cohen-Kedar et al. 2014).

Originally identified through recognition of an endogenous ligand on T-cells, Dectin-1 is best known for its ability to recognise β-1,3-glucans (Ariizumi et al. 2000; Drummond and Brown 2011). These carbohydrates are commonly found in the cell walls of fungi, and consequently, Dectin-1 has been found to play a key role in antifungal immunity. Indeed, Dectin-1 has been shown to recognise numerous fungal species including pathogens such as *Candida albicans*, *Aspergillus fumigatus*, *Coccidioides immitis* and *Pneumocystis carinii* (Hardison and Brown 2012; Viriyakosol et al. 2013). Although Dectin-1 is structurally similar to classical carbohydrate-binding CLRs, the receptor lacks the residues typically involved in sugar recognition, and the mechanisms by which Dectin-1 actually recognises β-1,3-glucans is unknown. It has been shown that the minimum unit ligand for Dectin-1 is between 11 and 13 glucose monomers and that the affinity of its interaction with these carbohydrates is influenced by side chain branching (Palma et al. 2006; Adams et al. 2008). Structural and mutation analyses have

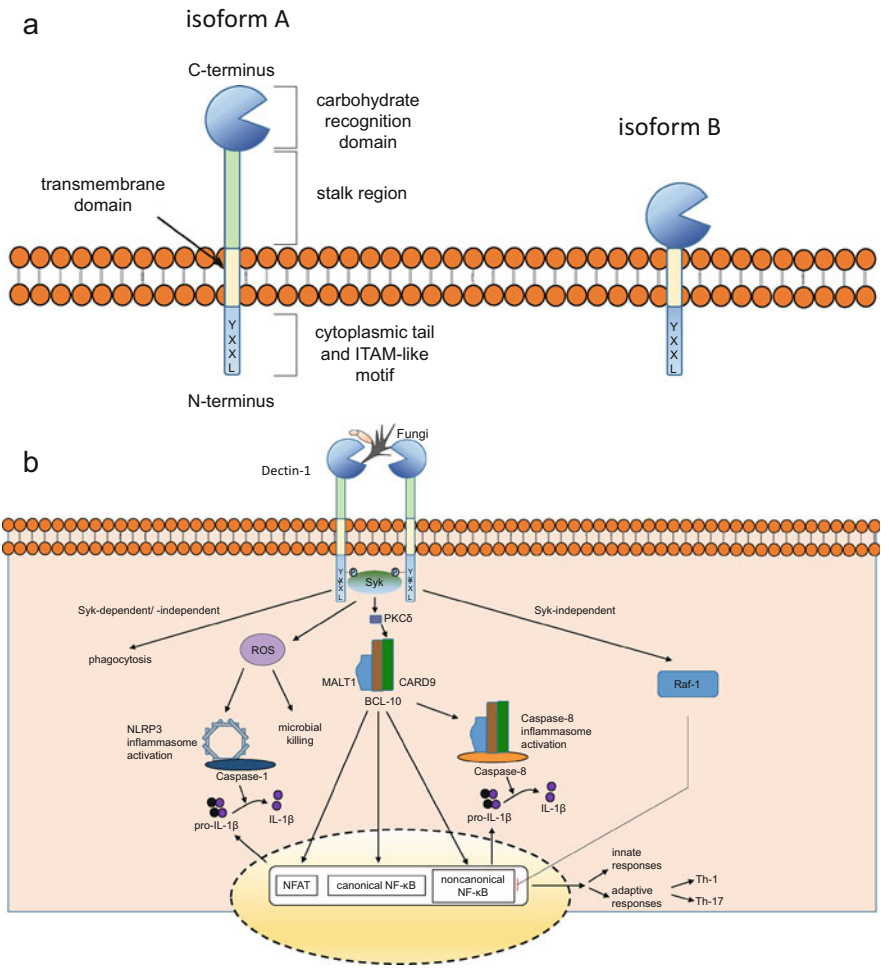

Fig. 4.1 Dectin-1 recognises β-glucan on fungi and mediates signalling through Syk-dependent and Syk-independent pathways. (**a**) Dectin-1 consists of a single carbohydrate recognition domain, a stalk region, a transmembrane and a cytoplasmic tail that contains an ITAM-like motif. Dectin-1 has two major isoforms in mice and humans, isoform A and isoform B, and six minor isoforms (not shown). These two isoforms differ in the presence of the stalk region. (**b**) Upon recognition of β-glucan on fungi, Dectin-1 mediates Syk-dependent NFAT and NF-κB pathways and the Syk-independent Raf-1 pathway to promote the production of cytokine and chemokine productions which in turn promotes antifungal defence through Th1 and Th17 responses. In addition, Dectin-1 signalling also promotes early release of arachidonic acid and eicosanoid production. Dectin-1 also mediates antifungal responses through phagocytosis, reactive oxygen species (ROS) production and inflammasome activation, which are essential in the cleavage and activation of inactive pro-IL-1β to active IL-1β

revealed a shallow groove on the surface of Dectin-1, which may be the ligand-binding site, and that this groove is flanked by two resides, Trp221 and His223, that are indispensable for ligand binding (Adachi et al. 2004; Brown et al. 2007). Dectin-1 can interact with other pathogens, but the structures involved are unknown (discussed below).

In addition to microbial pathogens, there is evidence that Dectin-1 interacts with endogenous ligands. Dectin-1 has been reported to bind the intermediate filament protein, vimentin, through which the receptor may be involved in driving lipid oxidation in atherosclerosis (Thiagarajan et al. 2013). Dectin-1 was also shown to be required for reverse transcytosis of secretory IgA-antigen complexes by intestinal M cells and the induction of subsequent mucosal and systemic antibody responses (Rochereau et al. 2013). In addition, Dectin-1 was shown to recognise galactosylated IgG1, in part through association with FcgammaRIIB, which resulted in inhibition of complement-mediated inflammation (Karsten et al. 2012). Recently, Dectin-1 was found to recognise N-glycans present on the surface of tumour cells and play a role in antitumour immunity (Chiba et al. 2014).

4.2 Dectin-1 Intracellular Signalling and Cellular Responses

Upon recognition of β-glucans, the ITAM-like motif of Dectin-1 is phosphorylated by Src kinases leading to the activation of Syk-dependent and Syk-independent intracellular signalling cascades (Fig. 4.1b). The ability of Dectin-1 to induce Syk-dependent signalling pathways is unusual, in that it is mediated by a single phosphorylated tyrosine residue and is likely to require receptor dimerization (Rogers et al. 2005; Drummond and Brown 2011). Signalling through this pathway involves PKC delta and the CARD9-Bcl10-Malt1 complex and leads to the induction of canonical and non-canonical NF-κB subunits (p65/c-REL and RelB, respectively) and interferon regulatory factor (IRF) 1, resulting in gene transcription (Drummond and Brown 2013; Wevers et al. 2014). Recently, however, CARD9 was found to be dispensable for NF-κB activation, but regulated extracellular signal-regulated kinase (ERK) activation by linking Ras-GRF1 to H-Ras (Jia et al. 2014). Syk activation by Dectin-1 also induces IRF5 and nuclear factor of activated T-cells (NFAT), through phospholipase C gamma and Calcineurin; a pathway inhibited by immunosuppressive drugs, such as cyclosporine (Goodridge et al. 2007; del Fresno et al. 2013). The Syk-independent pathway from Dectin-1 involves activation of Raf-1, which integrates with the Syk-dependent pathway at the point of NF-κB activation (Gringhuis et al. 2009). The ability of Dectin-1 to induce productive intracellular signalling (i.e. leading to cellular responses) requires receptor clustering into a 'phagocytic synapse' and exclusion of regulatory tyrosine phosphatases (Goodridge et al. 2011). Moreover, the ability of Dectin-1 to induce productive responses to purified agonists can be cell-type specific, an effect

linked to differential utilisation of CARD9 (Rosas et al. 2008; Goodridge et al. 2009).

Activation of Dectin-1 signalling pathways can induce or regulate multiple cellular responses including actin-mediated phagocytosis, neutrophil extracellular trap (NET) formation, activation of the respiratory burst and DC maturation and antigen presentation, in part through the use of autophagy machinery such as light chain 3 protein (LC3) (Drummond and Brown 2011; Hardison and Brown 2012; Ma et al. 2012; Branzk et al. 2014). This latter process was recently shown to involve the FYVE and coiled-coil domain containing 1 (FYCO1) protein, which facilitated the maturation of Dectin-1 induced phagosomes (Ma et al. 2014). Dectin-1 also induces the production of eicosanoids, several cytokines and chemokines (such as TNF, IL-10, IL-6, IL-2, IL-23, IFN-β, CCL2, CCL3) and can modulate cytokine production induced by other PRRs (see later) (Drummond and Brown 2011; del Fresno et al. 2013). Dectin-1 is able to activate inflammasomes, facilitating the production of IL-1β. Indeed, this receptor activates the NLRP3/caspase-1 inflammasome upon recognition of β-glucans, in a Syk-dependent manner (Drummond and Brown 2011; Ganesan et al. 2014). Dectin-1 can also directly induce a non-canonical caspase-8 inflammasome through Syk, CARD9, MALT1 and the non-receptor tyrosine kinase Tec (Gringhuis et al. 2012; Zwolanek et al. 2014). Although most cellular responses described here involve signalling through Syk, this is not always the case in all cells. The induction of phagocytosis by Dectin-1 in macrophages, for example, does not require Syk but rather Bruton's tyrosine kinase (Btk) and Vav-1 (Herre et al. 2004; Strijbis et al. 2013).

4.3 Dectin-1 in Antifungal Immunity

Dectin-1 plays an essential role in antifungal immunity in both mouse and human. Polymorphisms of human Dectin-1, such as the Y238X polymorphism which results in a truncated protein that is not expressed at the cell surface, have been linked to increased susceptibility to infections with *A. fumigatus*, *Trichophyton rubrum* and *C. albicans* (Ferwerda et al. 2009; Cunha et al. 2010). However, the high prevalence of this polymorphism in European and African populations does not correlate with disease prevalence, suggesting that there are other factors contributing to susceptibility in affected individuals (Ferwerda et al. 2009). This likely explains the lack of an effect of the Y238X polymorphism on fungal susceptibility that has been reported in other studies. Deficiency of CARD9 on the other hand, renders both humans and mice extremely susceptible to fungal infection highlighting the importance of this pathway in antifungal immunity (Hardison and Brown 2012). In mice, Dectin-1 is required for protective immunity to several pathogens including *C. albicans*, *A. fumigatus*, *Pneumocystis carinii*, *Coccoidiodes posdasii* and most recently *Paracoccidioides brasiliensis* (Loures et al. 2014; Dambuza and Brown 2015). Notably, the requirement for Dectin-1 in protective immune

responses is dependent on fungal strain, at least in mouse models of candidiasis (Marakalala et al. 2013).

The increased susceptibility to fungal infections caused by Dectin-1 deficiency results from defective innate and adaptive antifungal immune responses. Indeed, loss of Dectin-1 correlates with aberrant or defective cellular responses such as fungal phagocytosis and killing, inflammasome activation and induction of inflammatory mediators. Recently, for example, NETs were shown to be selectively released in response to large non-ingestible fungal hyphae (Branzk et al. 2014). Dectin-1 acted as the sensor of microbial size, reducing NET formation following phagocytosis of smaller-sized yeasts, and loss of this receptor led to aberrant NET release and pathology (Branzk et al. 2014). Another example is the autophagy machinery where Dectin-1 induces the phagosomal recruitment of LC3, an autophagic factor required for the fungicidal activity of leukocytes. Loss of Dectin-1 led to failure of LC3 recruitment and reduced fungal killing (Kyrmizi et al. 2013; Tam et al. 2014).

Like the TLRs, Dectin-1 is capable of instructing the development of adaptive immune responses, particularly Th1 and Th17 immunity (LeibundGut-Landmann et al. 2007; Drummond and Brown 2011). While Th1 responses are important for the control of systemic fungal infections, Th17 responses are critical for controlling fungal infections at the mucosa (Kashem et al. 2015). Indeed, a number of human diseases associated with chronic mucocutaneous candidiasis, including CARD9 deficiency, have been linked to alterations in components of the Th17 response (Hernandez-Santos and Gaffen 2012). Several studies have shown that Dectin-1 is required for Th17 polarisation during infection, such as during mucocutaneous infections with *C. albicans* (Drummond and Brown 2011; Kashem et al. 2015). How Dectin-1 promotes Th17 responses is incompletely understood, but involves MALT1-dependent activation of the NF-κB subunit c-REL, which is required for the induction of polarising cytokines, such as IL-1β (through activation of the inflammasome) and IL-23p19 (Drummond and Brown 2011; Gringhuis et al. 2011). The ability of Dectin-1 to drive these responses is dependent on the specific morphology of *C. albicans* (i.e. yeast versus hyphae) (Drummond and Brown 2011; Kashem et al. 2015). Expression of Dectin-1 on lymphocytes, such as γδ T-cells, provides an important innate source for the rapid production of IL-17 and other key cytokines during infection (Martin et al. 2009; Drummond and Brown 2011). Dectin-1 can induce humoral responses, stimulate cytotoxic T-cell responses and induce Th17 cells in response to some fungi, such as *Paracoccidioides brasiliensis* (Drummond and Brown 2011; Loures et al. 2014). Triggering of Dectin-1 can induce innate memory (or trained immunity), through the epigenetic reprogramming of monocytes and the induction of neutrophilic myeloid-derived suppressor cells (Quintin et al. 2012; Rieber et al. 2015).

Fungal pathogens have evolved several mechanisms to avoid immune recognition by Dectin-1. For example, the surface conidial hydrophobin layer and cell wall galactosaminogalactan mask Dectin-1 recognition of *A. fumigatus* (Carrion Sde et al. 2013; Gravelat et al. 2013). Changes in cell wall structure during fungal morphological switching can reduce immune recognition by Dectin-1, such as

occurs with yeast versus hyphae in *C. albicans* (Gantner et al. 2005). In some pathogens, there is active masking of β-glucans upon infection, such as the switch to α-glucan production following infection with *Histoplasma capsulatum* (Rappleye et al. 2007). The differential exposure of fungal β-glucans can have substantial impact on host immunity, such as the allergic Th2 responses induced by intact *Cladosporium cladosporioides* (*C. cladosporioides*), which expose little of this carbohydrate at the surface (Mintz-Cole et al. 2012). In contrast, heat-killed *C. cladosporioides* and live *Aspergillus versicolor* both have exposed β-glucans and induce Dectin-1-dependent pulmonary Th17 responses (Mintz-Cole et al. 2012).

4.4 Role of Dectin-1 in Immunity to Other Pathogens

While Dectin-1 is best known for its role in antifungal immunity, it can recognise several other pathogens including *Haemophilus influenzae*, *Salmonella typhimurium*, *Mycobacterium tuberculosis* and *Leishmania infantum* (Drummond and Brown 2013; Lefevre et al. 2013; Heyl et al. 2014). For example, Dectin-1 was found to be required for the induction of macrophage microbicidal and inflammatory responses to *L. infantum* in vitro, and for the control pathogen growth in vivo (Lefevre et al. 2013). However, the role of Dectin-1 in immunity to most of these organisms is not well understood. For example, Dectin-1 was shown to be required for IL-12 responses to mycobacteria in vitro, but loss of this receptor had no effect on anti-mycobacterial immunity in vivo (Drummond and Brown 2013). How Dectin-1 even recognises any of these organisms is still unclear.

4.5 Interaction of Dectin-1 with Other PRRs

The recognition of pathogens by leukocytes involves multiple PRRs, which interact to promote pathogen-specific responses. Dectin-1 was one of the first receptors shown to be capable of such 'crosstalk'. For example, optimal responses to fungi requires signalling from both Dectin-1 and TLRs to synergistically induce the production of cytokines, such as TNF and IL-23, while repressing the production of others, such as IL-12 (Drummond and Brown 2013). Such interactions can be cell-type specific. For example, in DCs, Dectin-1 alone is sufficient for the production of TNF-α, whereas in macrophages, the production of this cytokine requires co-stimulation with TLRs (Drummond and Brown 2013). Dectin-1 interacts with other surface proteins, such as the tetraspanins CD63 and CD37, which regulate the surface expression and functional responses of Dectin-1 (Meyer-Wentrup et al. 2007). Other examples include the indirect activation of complement receptor 3 by Dectin-1, through Vav signalling, that is required for effective neutrophil anti-candida effector functions (Li et al. 2011).

Dectin-1 can interact with other CLRs. For example, an optimal Th17 response to *C. albicans* was found to require signalling from both Dectin-1 and Dectin-2 (Robinson et al. 2009). Dectin-1, in combination with TLR2, was shown to be able to amplify mannose receptor-induced IL-17 production (van de Veerdonk et al. 2009). However, these interactions can also have negative consequences. For example, engagement of the CLR mincle during chromoblastomycoses was recently shown to promote non-protective Th2 immunity by suppressing Dectin-1-mediated Th1 responses (Wevers et al. 2014).

4.6 A Broader Role for Dectin-1 in Immunity

There is emerging evidence that Dectin-1 plays a broader role in immunity. As discussed above, Dectin-1 recognises endogenous molecules, such as galactosylated IgG1 complexes, and regulates the subsequent immune responses induced by these ligands. Dectin-1 has been implicated in the regulation of autoimmune diseases, such as arthritis and colitis. For example, stimulation of Dectin-1 can trigger the development of severe chronic arthritis in genetically susceptible mice (Yoshitomi et al. 2005). In contrast, signalling from Dectin-1 was found to be required for the control of excessive inflammation induced by pathogenic fungi during ulcerative colitis (Iliev et al. 2012). These functions of Dectin-1 can have therapeutic potential, such as promoting innate memory described above. Other examples include administration of the Dectin-1 ligand, β-glucan, to protect against type 1 diabetes, enhance antitumor immune responses, promote wound healing, and CNS axon regeneration, for example (Tian et al. 2013; Karumuthil-Melethil et al. 2014; van den Berg et al. 2014; Baldwin et al. 2015). Even the CRD of Dectin-1 has been used to develop novel therapeutic strategies, when engineered into soluble fusion proteins or incorporated into chimeric T-cell receptors, for example (Ricks et al. 2013; Kumaresan et al. 2014).

4.7 Conclusion

Dectin-1 is one of the best studied receptors, yet we are still discovering new roles and functions for this archetypical PRR. Studies in mice and in humans have clearly demonstrated that the innate and adaptive immune functions mediated by this receptor play a key role in antifungal immunity. Less well understood is the role of Dectin-1 in autoimmunity and its broader immune functions in other infectious and noninfectious diseases. The ability of Dectin-1 to collaborate with other PRRs adds significant complexity yet will be key to fully understand the physiological roles of this CLR. Excitingly, our growing knowledge is already suggesting how Dectin-1 can be targeted or used to provide novel therapeutic strategies for the future.

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