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C-type lectins in immunity: recent developments

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C-type lectin receptors (CLRs) comprise a large superfamily of proteins, which recognise a diverse range of ligands, and are defined by the presence of at least one C-type lectin-like domain (CTLD). Of particular interest are the single extracellular CTLD-containing receptors of the 'Dectin-1' and 'Dectin-2' clusters, which associate with signalling adaptors or possess integral intracellular signalling domains. These CLRs have traditionally been associated with the recognition of fungi, but recent discoveries have revealed diverse and unexpected functions. In this review, we describe their newly identified roles in anti-microbial host defence, homeostasis, autoimmunity, allergy and their functions in the recognition and response to dead and cancerous cells.

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Introduction

C-type lectin receptors (CLRs) are normally associated with carbohydrate binding through conserved motifs present in the C-type lectin-like domain (CTLD), such as the EPN motif (which confers binding to mannose, *N*-acetylglucosamine, L-fucose, and glucose) and the QPD motif (which confers recognition of galactose and *N*-acetylgalactosamine) [1,2]. Yet CLRs also recognise carbohydrates, such as β-glucan, and many non-carbohydrate ligands, such as lipids and proteins, through mechanisms that are not yet fully understood [1,2]. CLRs are primarily expressed on myeloid cells where they perform various roles but effectively function as pattern recognition receptors (PRRs), activating or modulating immune function upon encountering ligands from 'non-self' (pathogen-associated molecular patterns — PAMPs), 'damaged self' (damage-associated molecular patterns — DAMPs) or 'altered self' (tumour-associated molecular patterns — TAMPs).

For the purposes of this review, CLRs can be clustered into two broad groups based on their signalling potential. Activation receptors transduce intracellular signals via an integral immunoreceptor tyrosine-based activation (ITAM)-like motif within their cytoplasmic tails (such as Dectin-1, Clec-2, and DNGR-1), or via association with ITAM-bearing FcRγ adaptor molecules (such as Dectin-2, CLECSF8 and Mincle) [3,4•] (see Table 1). Activation of these receptors leads to intracellular signalling through Syk-dependent and Syk-independent pathways [3], discussed later. The second group of CLRs possess immunoreceptor tyrosine-based inhibition (ITIM)-motif in their cytoplasmic tails (such as MICL), which recruit phosphatases including SHP-1, SHP-2 and SHIP upon receptor activation. Signalling from these receptors generally supresses cellular activation, including the activity of activation CLRs [4•]. Paradoxically, these inhibitory receptors can also act to enhance cellular responses in certain circumstances, by inhibiting inhibitory responses for example see [5].

Receptors of the 'Dectin-1' and 'Dectin-2' clusters of CLRs [6,7] (Figure 1) are of particular interest, and study of these receptors has provided startling new insights into the function and roles of CLRs in immunity and homeostasis. In this review, we will focus only on receptors in these two clusters, discussing the most recent discoveries. We will cover newly identified functions in host defence against fungi and bacteria and their emerging roles in homeostasis, autoimmunity, allergy and recognition of dead and cancerous cells. The reader is referred to other recent reviews for more in-depth details on the function and roles of each of the CLRs discussed here [4•,6,7].

CLRs in anti-fungal immunity

Much of the interest in CLRs has emerged from the discovery that these receptors play critical functions in anti-fungal immunity [8]. In fact our understanding of anti-fungal immunity has significantly increased over the last decade, and we now understand that Th1 effector cells are critical in anti-fungal immunity, particularly from systemic infections with pathogens such as *Cryptococcus neoformans* [9]. Th17-related immunity, on the other hand, is also critical, being recently demonstrated to be essential for protection at the mucosa [10]. Indeed, defects in several components of the Th17 pathway, from the signalling molecules (CARD9, STAT1, STAT3) to the cytokines involved (IL-17) have been linked to susceptibility to chronic mucocutaneous candidiasis [11]. CLRs, such as Dectin-1 and Dectin-2, play a central role in driving the development of these responses [8]. To date, however, only polymorphisms in Dectin-1 and

Table 1

Alternative names of CLRs discussed in this review

CLR mentioned in text	Aliases	Official gene symbol Human/mouse
Dectin-1	CLEC7A, CLECSF12, BGR, CANDF4	CLEC7A/Clec7a
CLEC2	CLEC1B, CLEC2B	CLEC1B/Clec1b
DNGR-1	CLEC9A	CLEC9A/Clec9a
Dectin-2	CLEC4N, CLEC6A, CLECSF10, Nkcl	CLEC6A/Clec4n
CLECSF8	CLEC4D, CLEC6, MCL, MPCL, Dectin-3	CLEC4D/Clec4d
Mincle	CLEC4E, CLECSF9	CLEC4E/Clec4e
MICL	CLEC12A, CLL-1, CLL1, DCAL-2, KLRL1	CLEC12A/Clec12a

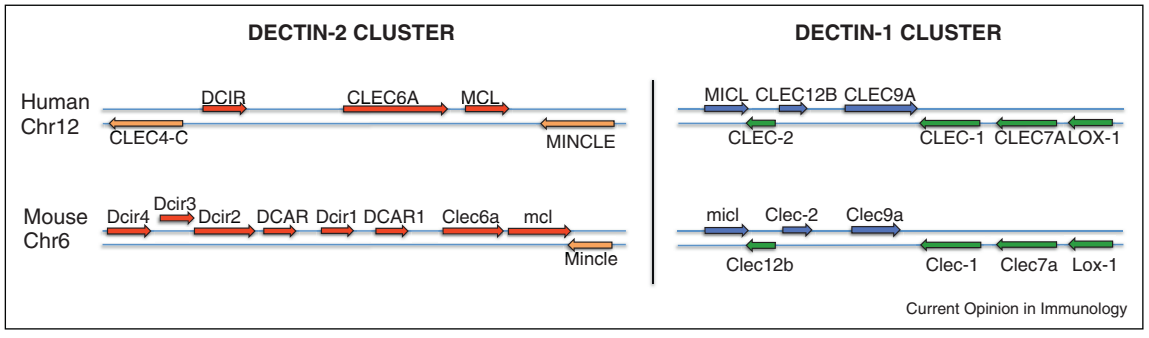
mutations in signalling molecule CARD9, which acts downstream of Syk-coupled CLRs (see below), have been linked to susceptibility to fungal infections in humans [12,13].

The study of Dectin-1, in particular, has revolutionised our understanding of host-fungal interactions. This CLR recognises β-glucans, a carbohydrate present in cell walls of many, if not all, fungal species, and is required for immunity to several pathogens including species of *Candida*, *Aspergillus*, *Pneumocystis* and *Coccoidiodes* [8]. Dectin-1 was discovered over a decade ago as the first non-Toll-like receptor capable of coupling microbial recognition with gene transcription, and there has been much interest in understanding its intracellular signalling mechanisms [14]. The activation of Dectin-1 requires receptor clustering into a phagocytic synapse [15••], which induces a signalling pathway now known to be common to all the activatory CLRs discussed here: tyrosine phosphorylation of the ITAM-like/ITAM motifs, recruitment and activation of Syk kinase and subsequent activation of the CARD9–Bcl10–Malt1 (CBM) scaffold through PKCδ [16]. Stimulation of this pathway by Dectin-1 and other Syk-independent pathways, such as that mediated by Raf-1, results in the activation of several transcription factors including NFAT, IRF1, IRF5, and the canonical and non-canonical subunits of Nf-κβ (p65, RelB, c-Rel, p50 and p52) [6,17–19]. Recently, Dectin-1 activation of CARD9 was shown to regulate H-Ras activation, through Ras-GRF-1 phosphorylation, leading to activation of ERK but not Nf-κβ [20] (Figure 2). Dectin-1 mediated signalling can also be supressed by co-engagement with other CLRs, such as Mincle, which was found to induce Mdm2-dependent loss of nuclear IRF1 activity, blocking Dectin-1 mediated *IL12A* transcription [19].

Signalling by Dectin-1 regulates numerous cellular responses including phagocytosis, autophagy, the respiratory burst, the production of inflammatory lipids and numerous cytokines and chemokines including Th17-polarising cytokines such as IL-23, IL-6 and IL-1β [8,21]. Dectin-1 induced production of IL-1β is notable, as it involves both the NLRP3/caspase-1 and non-canonical caspase-8 inflammasomes [17,22••,23]. Dectin-1 can also induce the production of type I interferons (IFNs) in response to *Candida albicans*, through IRF5, and was crucial for protective immunity in mice [24]. Another group, however, found that these cytokines contributed to susceptibility to infection with *C. glabrata* [25]. Importantly, in humans, there is now evidence that type I IFNs play a protective role, at least in immunity to *C. albicans* [26]. The demonstration that Dectin-1 signalling through the Raf-1 pathway was able to induce innate memory by epigenetically reprogramming monocytes is also a significant recent advance, with implications for future vaccine design [27••,28].

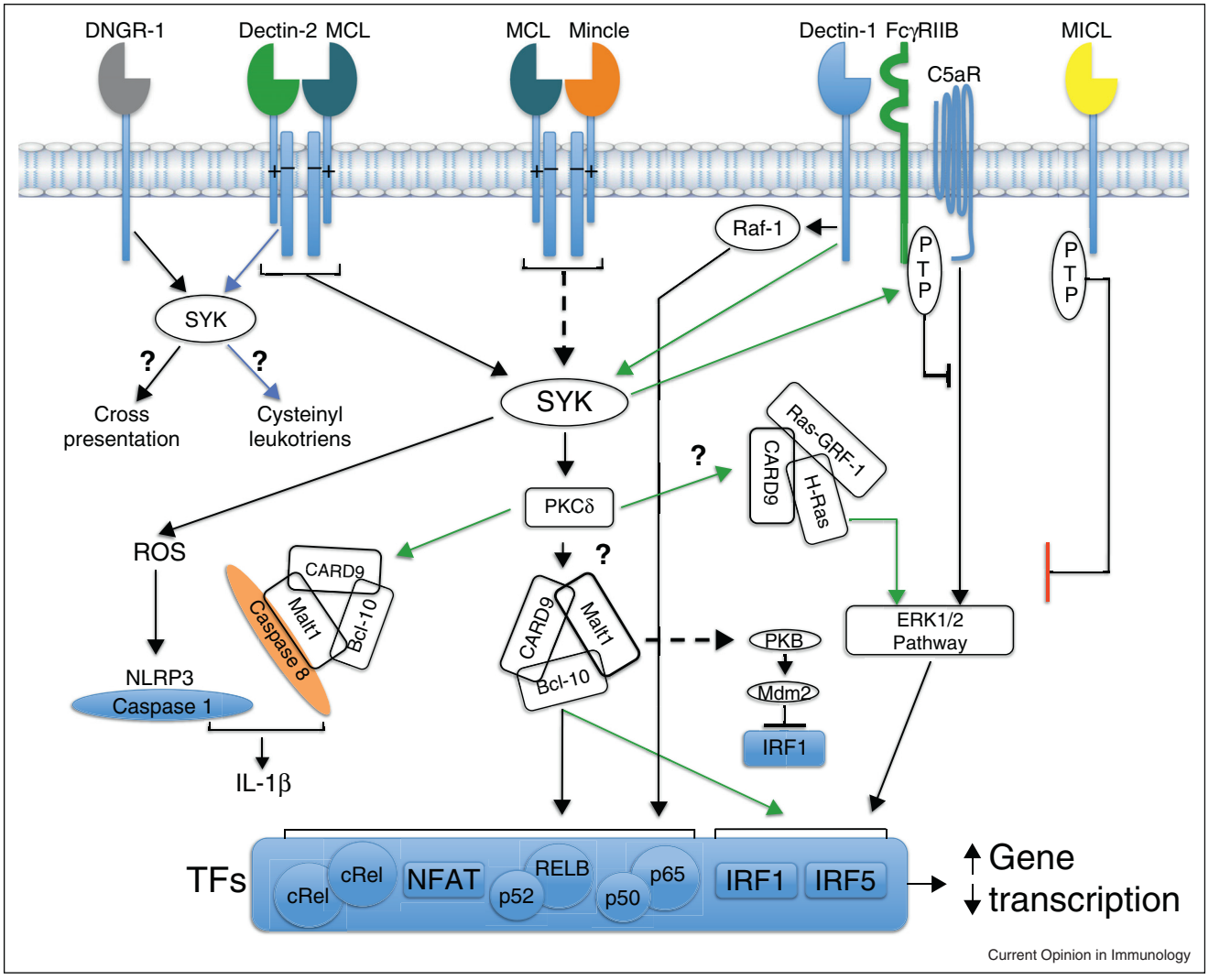
Other developments in this field involve Dectin-2, a CLR whose importance in protective anti-fungal immunity has been clearly demonstrated in animal models [7,29]. Dectin-2 recognises α-mannans from *Candida* and glycoproteins containing *O*-linked mannobiose-rich residues from

Figure 1



Organisation and orientation of transcription of the genes in the human and mouse 'Dectin-1' and 'Dectin-2' clusters. 'Dectin-1' cluster is in the centromeric part of the human NK gene complex in chromosome 12 (Chr12) and the corresponding region in the mouse is in chromosome 6 (Chr6), while the 'Dectin-2' cluster is encoded at the telometric end of the NK gene complex. Linkage, relative size and orientation of the genes are depicted.

Figure 2



Schematic representation of selected signal networks induced by various CLRs of the 'Dectin-1' and 'Dectin-2' clusters. Sensing of microbes by activatory CLRs such as Dectin-1, Dectin-2, Mincle and MCL mediate inflammation and immunity or antigen cross-presentation through activation of Syk-dependent and Syk-independent pathways (like the one mediated by Raf-1). Downstream signals from Syk leads to production of ROS and transcription factor activation by CARD9–Bcl-10–Malt-1 and more recently, CARD9–H-Ras–Ras-GRF1 complex. In some instances, activation of Syk by activatory CLRs like Dectin-1 can attenuate inflammatory signals by activating protein tyrosine phosphatases (PTP: SHIP, SHP-1 and SHP-2), which are recruited to inhibitory receptors such as MICL and FcγRIIB. Signals emanating from specific CLRs are depicted: Dectin-1 (green arrows), Dectin-2 (blue arrows) and Mincle (dashed black arrows). Question marks depict unknown or unclear pathways.

Malassezia [7,30]. Signalling from Dectin-2 induces several responses including the production of cytokines and chemokines [7]. Dectin-2 promotes Th17-biased immunity in response to fungi through the differential activation of cRel containing NF-κβ dimers by Malt1, and the preferential induction of IL-23p19 and IL-1β but not IL-12p40 [17]. It is likely that simultaneous engagement with other PRRs is required for amplification of such responses and the recent description of a Dectin-2/CLECSF8 heterodimer with enhanced sensitivity to α-mannans on *C. albicans* supports this notion [31] (Figure 2). Dectin-2 signalling also augments IL-17RC expression in neutrophils, and is involved in an autocrine IL-17A-IL-17RC feedback loop that is important for ROS production and fungal elimination [32•].

CLRs in anti-mycobacterial immunity

In addition to fungi, there is increasing realisation that CLRs play a key role in defence against bacterial infection. CLRs have been implicated in the recognition of several bacterial pathogens [16], but most interest has focused on their role in anti-mycobacterial immunity.

Indeed, several CLRs recognise mycobacteria including Dectin-1, Mincle and most recently CLECSF8 and Dectin-2 [33–35]. In fact, the activity of Complete Freund's Adjuvant (CFA), a mycobacterial-based adjuvant widely used in experimental models, was shown to require signalling through Mincle [36]. CLECSF8, like Mincle, recognises mycobacterial cord factor (trehalose dimycolate, TDM) driving pro-inflammatory innate responses and the development of Th17 immunity [33,34]. CLECSF8 was also required for induction of Mincle following TDM stimulation [34], leading to the formation of functional heterodimers [37].

Dectin-2 recognises mannose-capped lipoarabinomannan (Man-LAM) and like the other CLRs, induces cytokine production and induction of Th17 responses [35]. Despite the ability of all these CLRs to recognise and respond to mycobacterial components the role of these receptors during infection is still unclear. Most appear redundant or show limited defects during infection, and no links with human disease have yet been described [33,35,38–40]. The substantially increased susceptibility of CARD9 knockout mice to mycobacterial infection [41•], however, shows that signalling from these receptors is required for protection. Presumably these CLRs are able to compensate for each other during infection.

CLRs in homeostasis, autoimmunity and allergy

Like many other PRRs, there is increasing evidence that CLRs can regulate immune homeostasis, autoimmunity and allergy. For example, treatment of mice with the Dectin-1 ligand, β-glucan, provides protection from type-1 diabetes but can also induce arthritis in susceptible mice [42,43]. Dectin-1 can inhibit inflammation induced by the complement component, C5a, in the presence of glycosylated IgG1–immune complexes. This mechanism involves Syk-mediated phosphorylation of FcγRIIB and the subsequent activation of Src homology 2 domain-containing inositol phosphatase (SHIP) [44]. Another recent example is Clec-2, which recognises podoplanin, and interactions with this ligand are required for DC motility along stromal surfaces and for the development of lymphatic vasculature and lymph nodes [45–48].

There is growing literature on the importance of these CLRs in immune homeostasis of the gastrointestinal tract. Dectin-1 is essential for facilitating the reverse transcytosis of secretory IgA complexes by intestinal microfold (M) cells [49] and is involved in promoting tolerogenic signals in response to mucus [50••]. The sensing of mucus (specifically MUC2) in the small intestines involves a complex of galectin-3, Dectin-1 and FcγRIIB on antigen-sampling dendritic cells which activates β-catenin and inhibits NF-κβ-mediated pro-inflammatory gene expression [50••]. The ability of Dectin-1 to sense mycobiota is also important for gut homeostasis, as loss of this receptor leads to fungal-mediated exacerbation of inflammation in murine models of colitis [51••]. Moreover, polymorphisms of Dectin-1 were found in patients with severe ulcerative colitis, suggesting that anti-fungals could be used to treat these individuals [51••].

CLRs also initiate and modulate allergic responses. Dectin-1, for example, promotes immunopathology during fungal allergy [52]. Most interest, however, has focussed on Dectin-2, which induces cysteinyl leukotriene production in response to HDM [53]. The production of these lipid mediators, as well as IL-33, is essential for the initiation of airway inflammation and promotion of subsequent Th2 immunity in response to HDM [53–56]. In murine models, Dectin-2 is involved in the development of allergic responses to HDM during both the sensitisation and challenge stages [57,58].

CLRs in the recognition of dead cells and tumours

CLRs, including Mincle, DNGR-1 and MICL, can sense cell death [59]. Mincle was the first such receptor identified, and shown to induce pro-inflammatory responses after sensing SAP130 released from dead cells [60]. This ability to detect and respond to dead cells has recently been linked to pathogenic responses induced after ischaemic stroke and traumatic brain injury [61,62].

DNGR-1 is expressed by specific subsets of DCs and recognises F-actin exposed on necrotic cells [63,64•,65•]. Although this receptor possesses an ITAM-like motif in its cytoplasmic tail, it does not induce pro-inflammatory responses [64•]. Rather, signalling from this receptor is required for antigen cross-presentation [66••]. The mechanisms involved are incompletely understood, but essential for antiviral immunity [67,68].

Myeloid inhibitory C-type lectin-like receptor (MICL, CLEC12A, CLL-1) is the newest 'kid' on the block and recognises uric acid and proteinaceous ligand(s) on necrotic cells [69•]. MICL functions as an inhibitory receptor, blocking signalling from Syk-coupled activation receptors, and loss of this CLR results in hyperinflammation in the presence of cellular necrosis [69•]. MICL is also highly expressed on most acute myeloid leukaemias and, although its function on these cells is unknown, it has been suggested to be a useful marker of this disease [70].

CLRs have long been associated with immunity to cancer, particularly those receptors expressed on NK cells and involved in the recognition of MHC molecules. Very recently, Dectin-1 has been implicated in NK-mediated killing of tumour cells [71••]. Here, Dectin-1 expressed on DCs and macrophages was shown to recognise *N*-glycans present on the surface of tumour cells, triggering IRF5 nuclear translocation and induction of several genes including *Inam*, known to enhance tumour killing by NK

cells through homophilic interactions [71••]. More work is required to determine the nature of the ligands involved, and how they interact with Dectin-1. Nevertheless, these observations have exciting clinical implications and may explain, at least in part, the anti-tumour activities of β-glucans [72]. It is tempting to speculate that other CLRs in the 'Dectin-1' and 'Dectin-2' clusters may similarly be involved in such responses.

Concluding remarks

Recent data on the 'Dectin-1' and 'Dectin-2' cluster of CLRs have provided astonishing new insights into their roles and functions in immunity and homeostasis. These receptors, which are conserved in all chordates [73], are able to trigger numerous cellular and immunological responses critical for the control and regulation of infection, homeostasis, autoimmunity, allergy and cancer. CLRs offer tremendous potential to enhance the efficacy of vaccines and as therapeutic targets in infectious and non-infectious diseases. Yet, we are only beginning the voyage of discovery and there is much we still need to understand. Critical questions remain, such as understanding how CLR responses are negatively regulated (this is almost completely unstudied), understanding how responses from multiple CLRs and other PRRs are integrated, and understanding how polymorphisms and mutations in CLRs contribute to human disease.

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