REVIEW

C-type lectin receptors of the Dectin-1 cluster: Physiological roles and involvement in disease

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C-type lectin receptors (CLRs) are essential for multicellular existence, having diverse functions ranging from embryonic development to immune function. One subgroup of CLRs is the Dectin-1 cluster, comprising of seven receptors including MICL, CLEC-2, CLEC-12B, CLEC-9A, MelLec, Dectin-1, and LOX-1. Reflecting the larger CLR family, the Dectin-1 cluster of receptors has a broad range of ligands and functions, but importantly, is involved in numerous pathophysiological processes that regulate health and disease. Indeed, these receptors have been implicated in development, infection, regulation of inflammation, allergy, transplantation tolerance, cancer, cardiovascular disease, arthritis, and other autoimmune diseases. In this mini-review, we discuss the latest advancements in elucidating the function(s) of each of the Dectin-1 cluster CLRs, focussing on their physiological roles and involvement in disease.

Introduction

C-type lectin receptors (CLRs) play essential roles in immunity and homeostasis [1]. Comprising a family of more than 1000 proteins that each contain at least one C-type lectin-like domain, CLRs have been placed into 17 groups based on their structure and/or function. Originally named for their dependence on Ca^{2+} ions for carbohydrate recognition, many CLRs also possess conserved residues within their C-type lectin-like domains, such as the QPD (Gln-Pro-Asp) and EPN (Glu-Pro-Asn) motifs, which confer specificity for galactose and mannose-containing carbohydrates, respectively. However, CLRs can lack these components and still recognise sugars, as well as broader repertoire of ligands such as proteins and lipids [1].

The Dectin-1 cluster forms part of one subgroup of CLRs (group V), which consists of seven structurally related receptors, all with a single carbohydrate recognition domain, that are all encoded in the same locus in both the mouse and human genome [2] (Fig. 1). The receptors in this cluster are of particular interest, as they were the first signalling CLRs to be identified on myeloid cells, and none appear to require calcium to recognise their ligands. These receptors, which include MICL, CLEC-2, CLEC-12B, CLEC-9A, MelLec, Dectin-1 and LOX-1 (ordered based on genomic location), are involved in a broad range of physiological activities, from embryonic development to immunity. Importantly, the knowledge we are gaining from these receptors is opening exciting new possibilities for the diagnosis and treatment of disease. This mini-review, an update on our previous review of the Dectin-1 cluster [2], is aimed to provide an overview of each of these receptors, focusing on research published since 2016, highlighting the recent advancements made uncovering their functions.

MICL

Myeloid inhibitory C-type lectin-like (MICL, CLEC-12A, CLL-1, DCAL-2, KLRL-1), as the name suggests, is primarily expressed by

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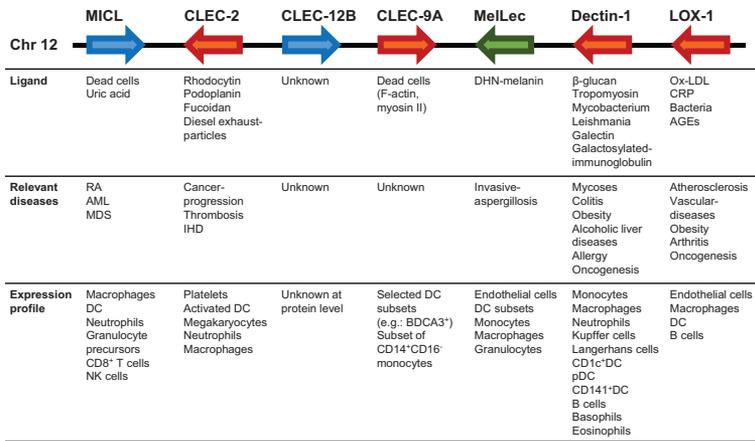
Figure 1. The Dectin-1 cluster of C-type lectin receptors. Shown is the genomic structure and transcriptional direction (arrows; blue = inhibitory CLR, red = activation CLR, green = unknown) of the Dectin-1 cluster of C-type lectin receptors found on human chromosome 12. The structure of the murine Dectin-1 cluster on mouse chromosome 6 is similar (not shown). Also shown are selected ligands for each receptor, as well as the relevant diseases and/or pathological conditions that have been associated with these CLRs. The cellular expression profile for the human receptors is also shown. AGE, advanced glycation end-products; AML, acute myeloid leukaemia; BDCA, Blood dendritic cell antigen; CD, cluster of differentiation; CRP, C-reactive protein; DHN, 1,8-dihydroxynaphthalene; IHD, ischemic heart diseases; MDS, myelodysplastic syndromes; Ox-LDL, oxidised Low Density Lipoprotein; RA, rheumatoid arthritis.

myeloid cells, including granulocytes and monocytes in humans and mice. MICL possesses an ITIM in its cytoplasmic tail, which can recruit Src homology region 2 domain-containing phosphatase-1 (SHP-1) and SHP-2, and through this pathway negatively regulates inflammatory cellular responses, including the respiratory burst [2] (Fig. 2). MICL has been implicated in antibacterial

autophagy and in regulating antibacterial NK cell cytotoxicity as well as cytokine production, DC migration across the blood brain barrier, antigen cross-presentation, and possibly a role in DC maturation [1–3].

Endogenous ligand(s) of MICL have been detected in various mouse tissues such as the heart, lung, liver, spleen, and kidney,
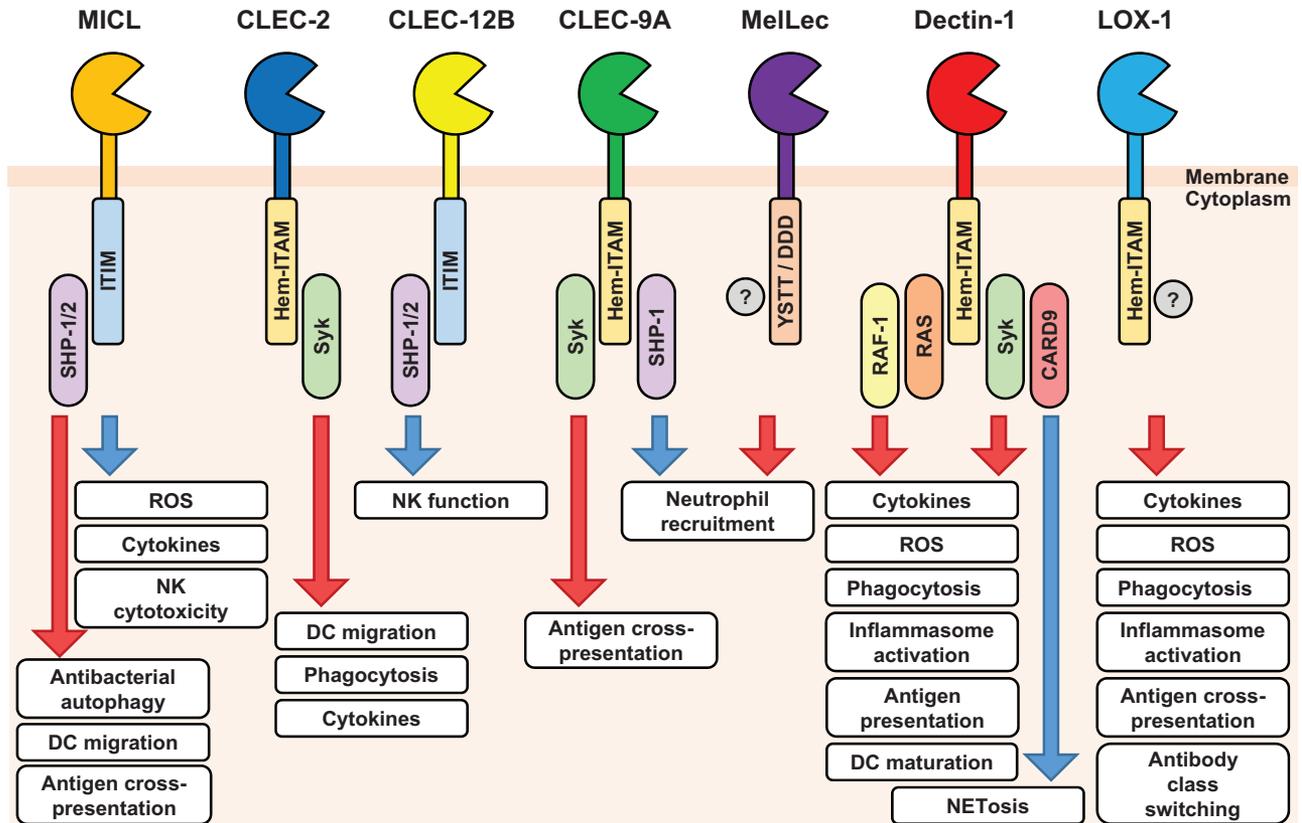
Figure 2. Representative signalling components utilized by the Dectin-1 cluster of C-type lectin receptors and selected cellular and immunological functions. The PAC-Man shape indicates the carbohydrate recognition domain, and the cytoplasmic motifs present in each receptor are indicated. Red arrows indicate cellular functions that are stimulated following receptor ligation while blue arrows indicate cellular functions that are repressed following receptor ligation. Receptors have been ordered based on their genomic localisation. Detailed signalling pathways are not shown. CARD, caspase recruitment domain-containing protein; NET, neutrophil extracellular traps; RAF, rapidly accelerated fibrosarcoma; Syk, spleen tyrosine kinase.

and recent studies show that this receptor senses dead cells [1, 2]. In fact, MICL recognises uric acid, a key danger signal for cell-death-induced immunity and MICL-deficient mice exhibit hyper inflammatory responses to necrotic cells. MICL-deficient mice also present with enhanced joint inflammation during a collagen antibody induced arthritis model, implicating the inhibitory functions of this receptor in the pathogenesis of rheumatoid arthritis. Although there are no genetic alterations linked to disease in humans, a subset of rheumatoid arthritis patients possess autoantibodies to MICL, which are able to exacerbate disease [4].

There has been considerable interest in human MICL in acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS), and this receptor represents a promising therapeutic and diagnostic target [5]. MICL is highly expressed on leukaemia stem cells, but not on normal hematopoietic stem cells, and high levels of MICL expression is correlated to poor prognosis [5, 6]. Immunotherapies for AML targeting MICL (including T cell recruiting bispecific antibodies and chimeric antigen receptor T cells) are being developed, and several are undergoing clinical trials [5].

CLEC-2

CLEC-2 (CLEC-1B) is expressed by platelets, megakaryocytes, and to a lesser extent by B cells and myeloid cells, including neutrophils, macrophages and subsets of DCs and has been largely studied in mouse models [1, 2]. Several ligands for CLEC-2 have been identified including rhodocytin (a protein present in snake venom), sulphated polysaccharides (such as fucoidan), diesel exhaust particles, and podoplanin (a mucin-type glycoprotein), although the biochemical basis underlying some of these interactions is still unknown [1, 2]. CLEC-2 had been implicated in recognition of HIV, but this recognition was subsequently shown to be indirect, through viral incorporation of podoplanin. Like other receptors in the Dectin-1 cluster, CLEC-2 possesses a hemi-ITAM in its cytoplasmic tail that mediates intracellular signalling though spleen tyrosine kinase (Syk)-dependent pathways (Fig. 2).

CLEC-2's expression on platelets has generated interest in its function in haemostasis and thrombosis. CLEC-2 plays a minor role during normal haemostasis, facilitating platelet adhesion in the vasculature, but under inflammatory conditions, it has a more major role in preventing bleeding, although this may be organ specific [7]. CLEC-2 is implicated in thrombosis, particularly during inflammation, which causes upregulation of podoplanin on stromal cells and macrophages [7, 8]. Interestingly, these activities of CLEC-2 appear to be independent of its ability to induce intracellular signalling through the Syk pathway [9].

CLEC-2 is involved in development, cancer, and immunity. In fact, CLEC-2 plays a critical role in embryonic development, facilitating blood-lymphatic separation, cerebrovascular patterning and integrity, lymph node and lung development, as well as platelet formation and the maintenance of hematopoietic stem cells in the bone marrow [1, 2, 10]. In cancer, the interaction of CLEC-2 with podoplanin-expressing tumour cells promotes angiogenesis, tumour growth and metastasis, and may represent a target for

therapy, if the side-effects on the haemostatic functions of the receptor can be overcome [11]. In contrast, expression of CLEC-2 on some cancer cells, such as gastric cancer cells, may be protective [12].

CLEC-2 is involved in DC migration and in the lymph node remodelling that is required for induction of adaptive immunity. During inflammation, CLEC-2 can also regulate leukocyte recruitment and activation, including adaptive responses, through interactions with podoplanin expressed by these cells [13–15]. Despite the considerable roles for CLEC-2 that have been gleaned from mouse models, the direct involvement of this receptor in human disease is yet to be described. However, plasma levels of soluble human CLEC-2, presumably generated by protease cleavage, as well as cellular expression levels are being explored as prognostic indicators of disease outcome (such as acute ischemic stroke [16] and cancer [17]).

CLEC-12B

By comparison with the other receptors in the Dectin-1 cluster, CLEC-12B (Macrophage Antigen H, MAH) is poorly characterised. Expression of a full length and spliced variant transcript, lacking exon 4 (encoding part of the C-type lectin-like domain, and presumably nonfunctional), was detected by RT-PCR in various human organs; however, only heart, kidney, liver, lung, spleen, and testis express the full length transcript [1, 2]. At the protein level, CLEC-12B has been detected on the human monocyte cell line, U937, following stimulation with phorbol 12-myristate 13-acetate, but the expression patterns of this receptor on mouse and human cells and tissues remain uncharacterised. CLEC-12B contains a classical immunoreceptor tyrosine-based inhibition motif in its cytoplasmic tail, that is able to recruit SHP-1 and SHP-2, and was able to inhibit NK cell function when transduced into these cells and following antibody crosslinking (Fig. 2).

Although its ligand(s) are unknown and its function is undefined, CLEC-12B is thought to interact with caveolin-1. In the context of disease, CLEC-12B is upregulated along with other immunosuppressive genes during the transition from the acute to asymptomatic stage during HIV infections, and it is part of a set of negative regulators upregulated in Behçet's Syndrome [18]. The presence of a polymorphism in *CLEC12B*, which may affect the secondary structure of the C-type lectin-like domain, has been linked in one family with predisposition to childhood cancer [19]. Suggestively, both SHP-1 and SHP-2 have also been linked to cancer, including melanomas, but more work is required to define the physiological role of CLEC-12B.

CLEC-9A

CLEC-9A (DNGR-1) is an endocytic receptor which recognises dead cells through exposed F-actin, a process which is enhanced by myosin II [20]. In humans, CLEC-9A is expressed on immature BDCA3+ DCs and on a small subset on CD14+CD16- monocytes,

and in the mouse, on CD8α+ conventional DC and plasmacytoid DCs. In fact, the expression profile of CLEC-9A has promoted its use both as a cellular marker and lineage tracer.

Structurally, CLEC-9A is very similar to Dectin-1, containing a hem-ITAM in its cytoplasmic tail that is able to induce intracellular signalling through Syk kinase (Fig. 2). Unlike Dectin-1, however, CLEC-9A does not appear to trigger cellular activation; rather induction of this signalling pathway promotes antigen cross-presentation to CD8+ T cells through a poorly defined mechanism involving pH-dependent conformational changes of the neck region of the receptor [21]. The cross-presentation activities of CLEC-9A have been shown in mice to be required for promoting protective CD8+ T cell responses to some (e.g. vaccinia virus, HSV), but not all (e.g. RSV), viral infections [1]. Notably, the ability of CLEC-9A to promote cross-presentation has prompted considerable interest in antigen targeting to this receptor to increase efficacy of cancer immunotherapies and vaccines [22].

Very recently, CLEC-9A has been discovered to restrict neutrophil recruitment during inflammation to limit tissue damage [23]. In mouse models of caerulein-induced necrotizing pancreatitis and systemic *Candida albicans* infection [23], activation of CLEC-9A by the cell death that occurred during inflammatory responses inhibited the production of the neutrophil-recruiting chemokine, MIP-2. Unexpectedly, this activity was found to be mediated through the recruitment of the inhibitory phosphatase, SHP-1, to the cytoplasmic tail of CLEC-9A (Fig. 2). The ability of CLEC-9A to limit neutrophil recruitment has also been observed in a mouse model of *Mycobacterium tuberculosis* infection [24]. In addition, there is also evidence from mice for involvement of this receptor in the regulation of inflammation during atherosclerosis [25]. As yet, there is no link between CLEC-9A and any human disease.

MelLec

Melanin sensing C-type Lectin receptor (MelLec, CLEC-1, CLEC-1A) was identified nearly two decades ago and is broadly expressed by endothelial cells in humans, mice, and rats. In humans and rats, this receptor is also expressed on myeloid cells, including various DC populations, monocytes, macrophages, and granulocytes [26]. MelLec was recently shown to recognise 1, 8-dihydroxynaphthalene melanin, an immunologically active component found in the cell wall of melanised fungi, such as *Aspergillus fumigatus* [27]. In mice, loss of MelLec led to decreased survival and increased fungal burdens in a systemic model of *A. fumigatus* infection through a delay in neutrophil recruitment [27]. Consistent with this observation, a polymorphism in the cytoplasmic tail of MelLec was associated with increased susceptibility to disseminated *Aspergillus* infections in stem-cell transplant patients [27].

MelLec has also been implicated in modulating T cell function [26]. In rats, the absence of MelLec led to exacerbated Th17 responses, which correlated with enhanced IL-12p40 expression by DCs [26]. Notably, decreased MelLec expression in human lung transplants was associated with increased levels of IL-17A and

chronic rejection [26]. Similar findings were also observed in rat allograft models. This suggests that MelLec may play a role in the tolerogenic response to allografts, through recognition of an unknown endogenous ligand [26]. How MelLec mediates its physiological functions is still unknown, although the receptor contains a YSST and tri-acidic DDD motif in its cytoplasmic tail that could potentially mediate intracellular signalling [2] (Fig. 2).

Dectin-1

Dectin-1 (CLEC-7A) is one of the best characterised CLRs in mice and in humans and is predominantly expressed on myeloid cells, including monocytes, macrophages, dendritic cells, and neutrophils [28]. Dectin-1 is also expressed by B cells in humans and by some subsets of T cells [1]. There is also some evidence for expression on other cell types, including epithelial cells [1, 29]. There are two major isoforms of Dectin-1 (one of which lacks the stalk region), and these show cell (and mouse strain) specific patterns of expression. Dectin-1 recognises β-glucans, carbohydrates commonly found in the cell walls of plants and fungi, but has also been reported to recognise tropomyosin (found in arthropods) and unidentified ligand(s) in mycobacteria and Leishmania [28, 30, 31]. Several endogenous ligands have also been identified including vimentin, galactosylated immunoglobulins, and galectins [28, 32].

Ligand recognition by Dectin-1 triggers intracellular signalling through a hem-ITAM in the cytoplasmic tail of the receptor that induces multiple downstream pathways, including Raf-1 and Syk/CARD9 (Fig. 2). Signalling from Dectin-1 can induce or regulate numerous cellular responses, including phagocytosis, the respiratory burst, neutrophil extracellular trap formation, autophagy, DC maturation and antigen presentation, inflammasome activation (including the NLRP3 and the non-canonical caspase-8 inflammasomes), and the production of eicosanoids, cytokines, and chemokines [28]. Dectin-1 is also capable of modulating the cellular responses induced by other pathogen pattern recognition receptors, can directly induce innate immune memory, and influence the development of CD4 and CD8 T cells and B cell responses [1, 33, 34].

Dectin-1 has been most studied in the context of anti-fungal immunity using mouse models. Indeed, through its ability to recognise β-1,3-linked glucan, Dectin-1 is required to drive protective host responses to many pathogenic fungal species, including *Aspergillus, Candida, Pneumocystis*, although its involvement may depend on particular strains of these organisms. Importantly, in humans, polymorphisms of Dectin-1 are associated with increased susceptibility to fungal disease [28]. The functions of Dectin-1 are also important for maintaining gastrointestinal homeostasis and can exacerbate the severity of colitis, through recognition specific fungi in the microbiota as well as food derived β-glucans [35–37]. Interestingly, Dectin-1 responses have been implicated in the pathogenesis of obesity [38] and alcoholic liver disease, following intestinal release of fungal β-glucans into the bloodstream [39].

More recently, Dectin-1 has been implicated in allergy and cancer. Although Dectin-1 is known to promote Th1 and Th17 immunity, this CLR can also drive Th2 responses, in part through the production of prostaglandin E2 [33]. Indeed, through this and other pathways, including regulation of IL-22 and IL-33, Dectin-1 has been linked to the pathology of allergic responses in both mouse models and in humans [30, 40]. Dectin-1 has dual functions in cancer, either promoting or preventing oncogenesis. For example, in pancreatic ductal adenocarcinoma, Dectin-1-mediated recognition of tumour-associated Galectin-9 supresses protective T cell responses [32]. In contrast, Dectin-1-mediated recognition of N-glycan structures on tumour cells can lead to activation of the tumoricidal activities of NK-cells. Dectin-1 can also mediate protective activities by supressing TLR4-mediated inflammation and by promoting Th9 immunity [1, 34].

LOX-1

Lectin-like oxidised low density lipoproteins (LDL) receptor-1 (LOX-1, OLR-1, CLEC-8A) is expressed on endothelial cells but also by a variety of other cell types including leukocyte populations (such as macrophages, monocytes, DCs, and B cells), smooth muscle cells, neurons, and fibroblasts [41]. Although normally expressed at low levels, in part through regulation by casein kinase 2-interacting protein-1 [42], LOX-1 is rapidly upregulated by a variety of factors, particularly pro-atherogenic stimuli including inflammatory cytokines and modified LDL. LOX-1 can be cleaved by ADAM10 proteases to produce a soluble form (sLOX-1) than is detectable in the serum, and N-terminal fragments that remain bound in the membrane [43]. LOX-1 is able to recognise a broad range of ligands including bacterial products, C-reactive protein, and advanced glycation end products, but is best known for its ability to bind oxidised LDL (ox-LDL). LOX-1 can internalize its ligands through a cytoplasmic tripeptide (DDL) motif, and induce intracellular signalling that results in a variety of cellular responses including the production of ROS, chemokines and cytokines, upregulation of adhesion molecules, apoptosis, as well as activation of the NALP3 inflammasome and NF-κB [44]. How LOX-1 mediates intracellular signalling is unclear, but recent evidence implicates the membrane N-terminal fragments in these activities, and their regulation by the signal peptide peptidase–like 2a and b (SPPL2a/b) [43].

LOX-1 has been extensively studied in the context of atherosclerosis and associated vascular diseases, including hypertension and stroke. Indeed, data from mouse models has convincingly demonstrated the role of LOX-1 in numerous pro-atherogenic activities including macrophage foam cell and plaque formation, endothelial dysfunction (such as increased ROS leading to activation of NF-κB and induction of adhesion molecules and apoptosis), proliferation of vascular smooth muscle cells, platelet aggregation, and leukocyte recruitment [41]. Notably, in humans, polymorphisms and alternative splice variants of LOX-1 gene are associated with either promotion or protection from disease [45]. Moreover, the levels of sLOX-1 can be used as a prognostic and diagnostic marker for car-

diovascular disease, and possibly stoke, in patients [41, 44, 46]. Given its detrimental activities, there is considerable interest in developing novel therapeutics that target LOX-1. Several drugs already in clinical use for treating cardiovascular disease appear to affect LOX-1, including statins, which disrupts LOX1-mediated recognition of oxLDL [41].

In the immune system, LOX-1 is able to regulate inflammatory responses to bacterial (including sepsis) and fungal pathogens. In fact, there is emerging evidence from mouse models that LOX-1 may represent a therapeutic target to treat *Aspergillus*-mediated keratitis [47]. LOX-1 is also involved in antigen cross-presentation (in part through the recognition of dead cells) and can promote B cell differentiation and antibody class switching. Moreover, targeting LOX-1 can promote antigen-specific T cell responses [48].

LOX-1 is involved in the pathophysiology of arthritis and cancer. In mouse models of arthritis and osteoarthritis, deletion of LOX-1 (which is upregulated on chondrocytes and other cells in affected joints) was shown to protect against disease [49, 50]. In humans, sLOX-1 has been proposed as a biomarker for diagnosis and evaluation of disease activity. Changes in lipid metabolism are associated with oncogenesis, and the activities of LOX-1 (which is upregulated in a wide range of cancers) in this context have been linked to promoting the development of cancer, including angiogenesis, tumour invasion, and metastasis [51]. Expression levels of LOX-1 have been proposed to have prognostic and therapeutic potential [52, 53].

Conclusion

Receptors of the Dectin-1 cluster have a wide range of functions and are involved in numerous diseases. In the last two decades, many important discoveries have been made regarding these receptors that have therapeutic implications. Indeed, characterisation of their structures, the identification of their ligands, and their signal transduction pathways has already led to new prognostic and diagnostic markers and novel immunotherapeutic approaches. It will be exciting to see how our ever-expanding knowledge of this C-type lectin subfamily is used to tackle disease in the future.

Conflict of interest: The authors declare no commercial or financial conflict of interest.

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Abbreviations: **AML**: acute myeloid leukaemia · **CLR**: C-type lectin receptor · **LDL**: low density lipoproteins · **MDS**: myelodysplastic syndromes · **MICL**: myeloid inhibitory C-type lectin-like

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