**C-type lectins in immunity and homeostasis**

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**Abstract**

The C-type lectins comprise a superfamily of proteins that recognise a broad repertoire of ligands and that regulate a diverse range of physiological functions. Most research attention has focused on the ability of C-type lectins to function in innate and adaptive antimicrobial immune responses, but these proteins are increasingly being recognised to have a major role in autoimmune diseases and to contribute to many other aspects of multicellular existence. Defects in these molecules lead to developmental and physiological abnormalities, as well as altered susceptibility to infectious and non-infectious diseases. In this Review, we present an overview of the roles of C-type lectins in immunity and homeostasis, with an emphasis on the most exciting recent discoveries.

The C-type lectins are a superfamily of more than 1,000 proteins that are defined by having one or more characteristic C-type lectin-like domains (CTLDs). They have been subdivided into 17 subgroups on the basis of their phylogeny and domain organisation1 (FIG. 1, Supplementary information S1 (table); and see also the Imperial College London C-type Lectins website [<http://www.imperial.ac.uk/research/animallectins/ctld/classes/C-type1.html>]). These molecules were originally named for their ability to bind carbohydrates in a Ca2+-dependent manner, through conserved residues within the CTLD, including the EPN (Glu-Pro-Asn) and QPD (Gln-Pro-Asp) motifs which confer specificity for mannose- and galactose-type carbohydrates, respectively1,2. However, the CTLDs of many C-type lectins lack the components required for Ca2+-dependent carbohydrate recognition and can recognise a broader repertoire of ligands including proteins, lipids and even inorganic molecules, such as ice1,2.

In mammals, C-type lectins are found as secreted molecules or as transmembrane proteins (FIG. 1), and they have been implicated in a diverse range of physiological functions through their ability to recognise self (endogenous) and non-self (exogenous) ligands. In fact, many C-type lectins can recognise both classes of ligand and are involved in numerous different physiological functions. Soluble C-type lectins can function, for example, as growth factors, opsonins, antimicrobial proteins and components of the extracellular matrix (ECM), and they regulate many essential processes such as development, respiration, coagulation, angiogenesis and inflammation. Transmembrane C-type lectin receptors (CLRs) can use various intracellular signalling pathways (BOX 1) to directly modulate cellular, developmental, homeostatic and immunological responses. The ectodomains of many transmembrane C-type lectins (such as the macrophage mannose receptor (MMR; also known as MRC1), attractin (ATRN), CD93 (also known as C1QR1) and thrombomodulin (THBD)) can also be shed and have extracellular functionality.

The past few years have seen considerable advances in our understanding of the role and functions of C-type lectins in mammalian immunity and homeostasis. Rather than providing an exhaustive description of each receptor, we summarize our current knowledge into a broad overview, citing examples where pertinent, but with a specific focus on the most exciting recent discoveries since 2014. We have subdivided this Review into discussions of homeostasis, cell death and cancer, as well as antimicrobial immunity and autoimmunity, preceded by a brief introduction to the expression of C-type lectins on immune cells. However, please note that we have made use of these subdivisions very loosely, to structure this Review, as these areas are often interrelated and overlapping, as are the functions of the C-type lectins involved.

**[H1] Immune cells and C-type lectins**

Cells of the innate and adaptive immune systems, including all myeloid cells and lymphocytes, express various C-type lectins (Supplementary information S1 (table)). Some are commonly expressed by leukocytes, such as L-selectin, which facilitates the adhesion of myeloid cells, such as neutrophils, to vascular endothelium as well as the trafficking of lymphocytes to secondary lymphoid tissues3,4. However, the expression of individual C-type lectins (or groups of related molecules) is often limited to specific cell lineages, and such receptors can function as useful lineage- or cell-type-specific markers. For example, dendritic cell (DC), natural killer (NK) cell lectin group receptor 1 (DNGR1; also known as CLEC9A) is expressed by DC precursors and can be used as a marker to identify human CD141+BDCA-3+ conventional (c)DC1s5-7. The expression of other C-type lectins is tightly regulated and they are only induced under particular conditions, such as inflammation8. These molecules can be useful as indicators of cellular state, such as CD69, which is rapidly expressed upon cell stimulation and is widely used as a marker to indicate the activation state of lymphocytes and NK cells9. There is also species specificity in the expression profiles of some C-type lectins (Supplementary information S1 (table)). For example, dectin 1 is predominantly expressed by myeloid cells in both humans and mice, but is additionally expressed on B cells (as well as a few other selected lymphocyte populations) in humans10.

**[H1] C-type lectins in homeostasis, cell death and cancer**

Whereas substantial research attention has focused on the role of C-type lectins in antimicrobial immunity and autoimmunity (see below), it is less well appreciated that these molecules have integral roles in all aspects of multicellular life, from patterning during embryonic development to the detection of abnormal cells, and that defects in these molecules can lead to developmental and physiological abnormalities, including cancer. Despite their importance, many of the C-type lectins that are involved in these activities are poorly characterised and our understanding of their contributions and underlying mechanisms remains incomplete. In this section, we have divided our discussion of the roles of C-type lectins into development and maintenance of normal physiology, the sensing of cell death and cancer. C-type lectins also have a role in maintaining homeostasis of the commensal microbiota, but that is discussed in later sections.

***[H3] Development and physiology***. Soluble and transmembrane C-type lectins carry out many diverse functions that are crucial for embryonic development and for the maintenance of normal physiology. For example, the collectins, such as surfactant protein A (SP-A; also known as SFTPA) and SP-D (also known as SFTPD) , are involved in respiration by regulating the surfactant layer that is required to reduce surface tension across the alveolar lining11. Other secreted C-type lectins constitute part of the ECM, such as the proteoglycans **[G]** versican (VCAN), aggrecan 1 (AGC1) and FRAS1-related extracellular matrix protein 1 (FREM1), and are involved in multiple essential processes. Versican, for example, is required for development of the heart and joints, but also for formation of the remodelled ‘provisional’ ECM which, together with hyaluronan, creates a hydrated matrix that facilitates cellular influx during inflammation, in part by facilitating the formation of chemokine gradients12. Tetranectin (also known as CLEC3B), which is present in the serum at high concentrations, enhances plasminogen activation, by facilitating its association with tissue plasminogen activator. Furthermore, tetranectin can bind fibrin, heparin and other sulphated polysaccharides, and is involved in osteogenesis, tissue remodelling and wound healing, although the underlying mechanisms involved are still unclear. Remarkably, mutations in this C-type lectin are associated with extreme longevity in humans13. Another member of the tetranectin family, CLEC11A (also known as osteolectin), was recently discovered to be an essential growth factor that promotes osteogenesis, and was found to be required for skeletal maintenance14. The transmembrane C-type lectin polycystic kidney disease 1 (PKD1) functions as a mechanosensor on primary cilia, in a complex with the structurally unrelated Ca2+-permeable cation channel PKD2, and mutations in PKD1 (or PKD2) result in autosomal dominant polycystic kidney disease **[G]**15. Interactions between the immunoreceptor tyrosine-based activation motif (ITAM)-coupled transmembrane C-type lectin CLEC2 (also known as CLEC1B) and the sialoglycoprotein, podoplanin, facilitate blood–lymphatic separation as well as cerebrovascular patterning and integrity during development16. Although the underlying mechanisms are still unclear, recent evidence indicates that these functions are independent of the signalling activities of either protein17,18. Moreover, the interaction of CLEC2 on DCs with podoplanin-expressing fibroblastic reticular cells **[G]** (FRCs) results in changes to actomyosin contractility in FRCs, which relaxes fibroblastic reticular network tension and facilitates the lymph node remodelling that is required for lymphocyte influx and proliferation during induction of an adaptive immune response19,20. C-type lectins are also involved in regulating the levels of circulating glycoproteins (for example, MMR and asialoglycoprotein receptor 2 (ASGR2) mediate glycoprotein uptake by endocytosis21), intravascular coagulation (for example, thrombomodulin binds thrombin and changes its substrate specificity for protein C22) and maintenance of haematopoietic stem cells (for example, by CLEC2 through the regulation of thrombopoietin production by megakaryocytes23), as well as energy homeostasis, hair pigmentation, monocyte–T cell interactions and central nervous system myelination (all of which involve attractin, although the underlying mechanisms are unknown but may involve its ability to function as a receptor for a dipeptidyl peptidase 24,25).

***[H3] Cell death***. C-type lectins are involved in the sensing and removal of dead and dying cells, which are crucial for maintaining tissue and organ homeostasis. Soluble C-type lectins, such as the collectins (mannose-binding lectin 1 (MBL1; also known as MBP-A and only found in mouse), MBL2 (also known as MBP-C), SP-A, SP-D and collectin 11 (also known as CL-K1)), can facilitate clearance of dead cells through recognition of exposed mannose structures, L-fucose, phosphatidylserine or nucleic acids. MBL, for example, opsonizes apoptotic cells for uptake by phagocytes and loss of this collectin results in defective clearance of dead cells *in vivo*26. Cell death can also be sensed by several membrane-bound CLRs, including oxidised low density lipoprotein receptor 1 (LOX1; also known as OLR1), MMR, DEC205 (also known as LY75), DC-SIGN-related protein 1 (SIGNR1; also known as CD209B), macrophage galactose lectin (MGL; also known as CLEC10A), myeloid inhibitory C-type lectin (MICL; also known as CLEC12A), DNGR1 and macrophage-inducible C-type lectin (mincle; also known as CLEC4E)27,28. Endogenous CLR ligands released from dead and/or dying cells (otherwise known as damage-associated molecular patterns (DAMPs)) include F-actin (which binds DNGR129), uric acid (which binds MICL28), and SAP130 and β-glucosylceramide (both of which are recognised by mincle30). The CLR-mediated cellular response triggered by these DAMPs depends on the nature of the receptor: for example, mincle induces inflammatory responses through the SYK–CARD9 (caspase-recruitment domain protein 9) pathway, whereas MICL inhibits SYK-induced cellular activation, through SHP1 and SHP227,28,30 (BOX 1). Inflammatory responses induced by mincle in response to DAMPs have been recently linked to alcoholic liver disease31, hepatitis32, obesity-induced adipose tissue fibrosis33, ischemia pathogenesis34, cancer35 and allergy36. By contrast, the recognition of cell death by DEC205 and DNGR1 promotes antigen presentation and cross-presentation, respectively. Both of these CLRs are influenced by pH, which indicates that receptor function can be modified by the intracellular environment following antigen uptake37,38. The physiological role of both of these receptors is still largely unclear, although cross-presentation activities mediated by DNGR1, which are induced through the SYK pathway27, are required for protection against certain viral pathogens (described below).

***[H3] Cancer***. Many C-type lectins, including DC-SIGN (also known as CD209), CD93, CLEC14A, MGL, CLEC2, MMR and the selectins, are able to support the interactions of cancer cells with platelets, leukocytes and endothelial cells, facilitating tumour invasion, metastasis and immune suppression39 (FIG. 2). For example, cancer cells expressing podoplanin can induce CLEC2-mediated platelet aggregation, which provides protection from leukocytes as well as shear stress, and which promotes angiogenesis, tumour growth and metastasis40. Expression of the homing receptor L-selectin facilitates lymphatic metastasis of cancer cells4, whereas systemic downregulation of this C-type lectin on naive T cells, by tumour-induced myeloid-derived suppressor cells **[G]** (MDSCs), disrupts T cell trafficking to secondary lymphoid tissues and the induction of a protective antitumour immune response41. Myeloid cell-expressed C-type lectins can similarly suppress immunity; for example, dectin 1 and mincle both promote pancreatic ductal adenocarcinoma through macrophage-induced repression of T cell responses following recognition of tumour-associated galectin 9 and SAP130, respectively35,42. Abnormal glycosylation patterns are a common feature of malignant cells, being associated with a poor prognosis, and direct detection of specific tumour-associated carbohydrates by C-type lectins, such as MGL and DC-SIGN, also induces immunosuppressive responses39. The undesirable consequences of C-type lectin activity in cancer have led to considerable interest in the development of therapeutics that target these receptors and their interactions with glycans.

In contrast to their detrimental activities, C-type lectins also mediate functions that are essential for anticancer immunity. In particular, the recognition of cellular transformation by NK cells crucially depends on C-type lectin-mediated sensing of alterations in the expression of MHC class I or MHC class I-like molecules, which induces activating or inhibitory intracellular signalling pathways (BOX 1) depending on the NK cell CLR that is engaged (FIG. 2). The integration of activating and inhibitory signals ultimately regulates NK cell responsiveness, although the sensitivity of individual NK cells is determined by their previous receptor ‘education’43. Whereas both mouse and human NK cells express the CD94–NKG2A heterodimeric inhibitory C-type lectin, the recognition of classical MHC class I molecules and induction of inhibitory NK cell signalling is mediated by entirely different receptors in mice and humans, which is suggestive of convergent evolution. In mice, these functions are mediated by the LY49 inhibitory C-type lectin family, whereas humans use members of the inhibitory killer cell immunoglobulin-like receptor (KIR) family. However, both human and mouse NK cells use similar activating C-type lectins, such as NKG2D, which recognises highly diverse and polymorphic MHC class I-related ligands, including MICA, MICB and UL16-binding proteins (ULBPs; also known as RAET1 proteins) such as ULBP1 (also known as MULT1). These ligands are induced on target cells following cellular stress, such as oncogenic transformation or viral infection (described below). Detection of NKG2D ligands by NK cells triggers their cytotoxic effector functions, through DAP10-associated (and, in mice, DAP12-associated) signalling pathways44 (BOX 1). Tumour cells are thought to be able to evade these responses by shedding NKG2D ligands to desensitise NK cells, although recent evidence suggests that shedding ULBP1 can restore NK cell activation and protective immunity45. Cancer cells can also induce the expression of NKG2D ligands by myeloid cells, for example through the secretion of lactate dehydrogenase, which results in the downregulation of NKG2D on NK cells and suppression of protective immune responses46.

Protective antitumour immunity also depends on the C-type lectins expressed by myeloid cells. For example, dectin 2 and macrophage C-type lectin (MCL; also known as CLEC4D) expressed on Kupffer cells were recently shown to help supress liver metastasis by facilitating the phagocytosis and clearance of cancer cells47. Dectin 1 is also protective during hepatocarcinogenesis, by suppressing Toll-like receptor 4 (TLR4) signalling and inflammation48. Dectin 1 can recognise selected N-glycan structures on tumour cells, triggering IRF5-dependent responses in DCs or macrophages that activate the tumoricidal activity of NK cells49. In fact, there is considerable interest in using the responses that are induced by these CLRs for immunotherapeutic intervention (BOX 2). For example, carbohydrate ligands of dectin 1, particularly fungal-derived β-glucan, have long been known to induce antitumour immune responses, and were recently shown to mediate their protective activities by promoting the apoptosis of MDSCs50 and by inducing antitumour IL-9-producing T cells51. Moreover, myeloid-expressed C-type lectins, including DEC205, DNGR1, MGL and MICL, have been explored as targets on DCs to promote antigen uptake and boost anti-cancer and other immune responses52. Aberrant expression patterns of these receptors in cancer can also function as diagnostic or prognostic markers of disease.

**[H1] C-type lectins in antimicrobial immunity**

Most research attention on C-type lectins has focused on their roles in antimicrobial immunity, as these molecules can function as pattern-recognition receptors (PRRs) **[G]** through their ability to recognise various glycan structures that are found on most microorganisms. Soluble C-type lectins, such as the collectins (SP-A, SP-D, MBL, collectin liver protein 1 (CL-L1; also known as collectin 10) and collectin kidney protein 1 (CL-K1; also known as collectin 11)), can function as opsonins that facilitate phagocytic uptake, activation of the complement pathway, modulation of inflammation, and inhibition or direct killing of a wide variety of microorganisms. The discovery of the β-glucan receptor, dectin 1, revealed that membrane-bound C-type lectins can trigger intracellular signalling and induce a wide range of cellular and immunological responses that have essential functions in antimicrobial immunity (FIG. 3). Their ability to direct the development of adaptive immunity (particularly T helper 1 (TH1), TH1753 and B cell54 responses) has been of considerable interest, because of their importance of these responses in the control of systemic and mucosal infections, respectively, and in autoimmunity (discussed below). In this section, we highlight the cellular functions modulated by C-type lectins as they relate to antimicrobial immunity, and then discuss the roles of these receptors in immunity to fungi, bacteria, viruses and parasites. Dectin 1 is one key example discussed here, as some of the most significant advances made with respect to the C-type lectins during the time frame of this Review have focused on this receptor.

***[H3] Modulation of cellular functions.*** Membrane bound CLRs can induce or regulate a remarkable diversity of cellular functions in leukocytes that are crucial for the induction of protective antimicrobial immune responses55 (FIG. 3). For example, non-opsonic recognition by CLRs such as dectin 1 can tether pathogens to the leukocyte cell surface and trigger intracellular signalling pathways (BOX 1) that induce actin-dependent microbial phagocytosis and that regulate the subsequent phagosomal maturation pathways56. In myeloid cells, CLRs are capable of inducing or regulating key antimicrobial effector mechanisms, such as the respiratory burst and the formation of neutrophil extracellular traps **[G]** (NETs). Notably, CLRs can induce the production of numerous cytokines, chemokines and immunomodulatory lipids, such as the eicosanoids. Moreover, through both direct and indirect mechanisms, CLRs can activate the NLRP3, NLRC4 or caspase 8 inflammasomes, leading to the production of IL-1β57. In general, the responses induced by CLRs are proinflammatory, such as the production of IL-6, tumour necrosis factor (TNF) and leukotriene C4; however, these receptors also induce the production of anti-inflammatory molecules, such as IL-10. In DCs, CLRs facilitate antigen presentation to CD4+ T cells and the cross-presentation of antigens to CD8+ T cells, and direct the development of adaptive immunity (mainly TH1, TH17 and T follicular helper (TFH) cell responses, although dectin 2 has also been shown to drive the development of TH2 cell responses58). Direct recognition of pathogens by CLRs expressed on lymphocytes, including γδ T cells59, NK cells60 and B cells61, can also induce the production of proinflammatory cytokines, as well as those normally associated with adaptive immune responses, such as IL-17. However, the impact of direct pathogen recognition by CLRs expressed on lymphocytes is still poorly understood. Lymphocyte-expressed CLRs also have a key role during viral infection (and cancer, see above) by triggering inflammatory and cytotoxic responses following the sensing of alterations in the expression of MHC class I or MHC class I-like ligands on target cells44.

***[H3] Immunity to fungi***. C-type lectins are well known for their ability to recognise the carbohydrate-rich cell walls of fungi and they are now accepted to have a central role in immunity to most fungal pathogens. The importance of C-type lectin-induced antifungal immune responses is highlighted by the increased susceptibility to infection resulting from polymorphisms in these receptors and downstream signalling components, including deficiency of the signalling adaptor CARD9 (BOX 1), which predisposes both humans and mice to severe mucosal and systemic fungal infections, including those of the central nervous system62. The CARD9 signalling pathway was discovered in the context of experimental fungal infection, which has also been used to identify other components of C-type lectin-mediated intracellular signalling pathways (reviewed in REFS53 and8). Recently discovered components include JNK and CBLB (an E3 ubiquitin ligase that targets dectin 1, dectin 2, MCL and SYK63-65), both of which inhibit protective antifungal immune responses and represent attractive therapeutic targets (BOX 2). Notably, the effect of JNK was to suppress the expression and functions of the low-affinity IgE receptor, CD23, which is itself a C-type lectin that was found to recognise fungal β-glucan and α-mannan66. Other newly identified components of C-type lectin-mediated signalling include the VAV proteins, which function as key proximal activators of the CARD9 pathway67, and the ubiquitin ligase TRIM62, which is essential for CARD9 activity68. Polymorphisms in both of these molecules impact human disease67,68. Whereas phosphatases, including SHIP1 and SHP1, commonly downregulate C-type lectin-mediated responses69,70 (and see later), SHP2 was unexpectedly discovered to have a key role in C-type lectin-mediated signalling and protective antifungal immunity by functioning as a scaffold to facilitate SYK recruitment71.

 Experimental fungal infections and/or use of isolated fungal components, such as zymosan, have provided major insights into the many cellular and immunological functions of C-type lectins (FIG. 3). Infections with *Candida albicans*, for example, have recently shown that responses induced by dectin 1 are required for the induction of neutrophilic MDSCs, which have a protective role during systemic infections72, and are essential for the development of fungus-specific CD4+ T cell responses in the gastrointestinal tract73. In fact, the responses induced by dectin 1 and other C-type lectins in response to intestinal fungi or their components have a key role in intestinal homeostasis and can regulate the severity of inflammatory bowel disease 55,68,74,75. These receptors have also been linked to the development of alcoholic liver disease76. Soluble C-type lectins, such as MBL, have also been implicated in intestinal homeostasis to commensal fungi77. Different fungal morphotypes (yeast versus hyphae) influence C-type lectin-mediated T cell differentiation, in a process that is dependent on the DC subset involved and impacts tissue specific anti-fungal immunity78. At a cellular level, recent discoveries have shown that dectin 1-mediated phagocytosis in neutrophils limits nuclear translocation of neutrophil elastase, resulting in a size-dependent regulation of NET formation in response to different morphological forms of *C. albicans* and other pathogens79. Interestingly, in response to hyphal forms of *Aspergillus* spp., dectin 2 (but not dectin 1) induced extracellular trap formation in plasmacytoid DCs, a cell type that is normally associated with the response to viral infection but that also apparently contributes to protective antifungal immunity80.

 There is considerable interest in determining the involvement of individual C-type lectins in immunity to specific fungal pathogens, the ligands that are recognised, and the effects of polymorphisms of these receptors on human disease (reviewed elsewhere55). However, our understanding of these topics has yet to fully incorporate the genetic and non-genetic factors influencing the antifungal immune responses in the host81, or the interspecies fungal diversity that considerably impacts host responses and the relevance of specific C-type lectins82. Another complicating factor is the extensive interaction that occurs between C-type lectins and other PRRs, following fungal recognition, which can enhance or suppress specific responses55. For example, the recognition of *Fonsecaea* spp. by mincle suppresses protective T cell responses that are induced by dectin 1 and dectin 2 during infection83,84. Fungi can also directly modulate host immunity by evading C-type lectin recognition; *Histoplasma capsulatum* achieves this through several mechanisms including enzymatically removing exposed β-glucans from the cell surface85.

***[H3] Immunity to bacteria***. The role of C-type lectins in antibacterial immunity has been best studied in the context of mycobacterial infection, and there is a long and growing list of soluble and membrane-bound receptors that recognise these microorganisms86. Several cell wall glycolipid ligands for C-type lectins have been defined, including trehalose dimycolate (TDM, which is recognised by mincle and MCL), phosphatidyl-inositol mannosides (which are recognised by DC immunoactivating receptor 1 (DCAR1; also known as CLEC4B1)) and mannose-capped lipoarabinomannan (which is recognised by dectin 2 and DC-SIGN), which primarily induce inflammatory and antimicrobial cellular responses through the SYK–CARD9 pathway in myeloid cells86-88 (BOX 1). The stimulatory capacity of these ligands, and their ability to promote T cell immunity, has prompted interest in their use as immunological adjuvants **[G]** (BOX 2). Indeed, the effectiveness of the widely used mycobacteria-based experimental adjuvant complete Freund's adjuvant (CFA) involves mincle-mediated responses to TDM89.

Despite their ability to induce robust responses to purified mycobacterial ligands, and their ability to respond to intact organisms *in vitro*, the role of individual CLRs in antimycobacterial immunity is less clear. Analysis of the impact of human polymorphisms on disease, as well as experiments in C-type lectin knockout mice, have largely failed to establish an essential role for any specific receptor in antifungal responses86, which suggests that there is extensive redundancy in mycobacterial recognition. However, differences in host population genetics and bacterial strain variation are likely to be key factors that are yet to be fully considered in this context90. The one exception is MCL, whose phagocytic functions were essential for protective immunity to *Mycobacterium tuberculosis* in both mice and humans, although this was established in only one patient cohort91. Interestingly, deficiency of CARD9 renders mice extremely susceptible to mycobacterial infection92, but similar susceptibility has not been observed in humans with functionally deficient mutants of this adaptor (Anne Puel, personal communication). C-type lectins can have an indirect regulatory effect, such as the ability of DC immunoreceptor (DCIR; also known as CLEC4A) to sustain type I interferon (IFN) production in DCs, which has a key role in modulating infection-driven inflammatory pathology and mycobacterial control93.

 C-type lectins are increasingly being implicated in the control of other bacterial infections and are now thought to have broader roles in immunity to these microorganisms. For example, mincle was discovered to be essential for resistance to infection with *Streptococcus pneumoniae*94and with *Klebsiella pneumoniae95*, as loss of this receptor in mouse models led to impaired microbial clearance and dysregulated inflammatory responses. CLEC5A was recently discovered to have an important role in mediating protective immunity to *Listeria monocytogenes,* by regulating NET formation and the production of reactive oxygen species and proinflammatory cytokines96. C-type lectins can also provide indirect protection against bacteria, such as the soluble collectin, SP-A, which inhibits the growth and adherence to urothelial cells of uropathogenic *Escherichia coli*97. C-type lectins also control the gastrointestinal bacterial microbiota, influencing homeostasis, and affect the development of inflammatory bowel disease. A genome-wide analysis revealed multiple host loci, including several C-type lectins, that affect the composition and function of the gut microbiome98. Several immunological ‘circuits’ have been described. For example, both dectin 1 and SIGNR3 (also known as CD209d) influence the function of regulatory T (Treg) cells induced by *Lactobacillus* spp. during experimental colitis. Dectin 1 has an indirect effect through the induction of antimicrobial peptides following recognition of β-glucan in food, which suppresses bacterial growth75, whereas SIGNR3 has an effect through direct interactions with the bacterial surface layer protein A99. DC-SIGN has been shown to recognise fucose-specific carbohydrates on the human gastric pathogen, *Helicobacter pylori*, which suppresses inflammatory responses and drives the development of TH2 cell-mediated immunity100. Contact between the epithelium and intestinal bacteria is also controlled by the REG3 family of soluble bactericidal C-type lectins, which form pores in Gram-positive cell membranes101.

***[H3] Immunity to viruses***. C-type lectins expressed by NK cells have a crucial role in antiviral immunity through the regulation of cytotoxic responses following sensing of virus-induced alterations in expression of MHC class I or MHC class I-like molecules on infected cells, which are similar to the changes that occur during oncogenic transformation (described above). An excellent example of this is provided by NKG2D, whose MHC class I-like ligands are tightly regulated in healthy cells through various mechanisms, including transcriptional repression through the action of histone deacetylases (HDACs)102. Expression of virus-encoded HDAC inhibitors, as occurs during herpesvirus infection for example, overcomes this transcriptional repression and induces the expression of NKG2D ligands, including ULBP1102. The importance of these recognition systems is underscored by the numerous strategies that viruses have evolved to subvert these defences, including inhibition of expression of NKG2D ligands at the surface of infected cells, the secretion of virus-encoded antagonists (including MHC class I-like molecules) that block interactions of NKG2D with its ligands, and suppression of NKG2D itself through modulation of host cytokine responses103.

 The recognition of viral glycoproteins by myeloid cell-expressed C-type lectins also has an important protective role, inducing antiviral responses such as uptake and degradation of virus particles and the induction of adaptive immunity. For example, the recognition of HIV glycoproteins by Langerhans cell-specific C-type lectin (langerin; also known as CD207) leads to virus uptake and degradation in Langerhans cells through a novel TRIM5α-dependent autophagy **[G]** pathway, transfer of virus antigens to DCs and the induction of protective cytotoxic T lymphocyte **[G]** (CTL) responses104,105. However, C-type lectin-mediated protection against viruses can be indirect, such as the DCIR-mediated suppression of damaging inflammatory responses during Chikungunya virus infection, or the induction of CTL responses through the cross presentation activities of DNGR1 (discussed above) that are required for the control of infections with vaccinia virus106and herpes simplex virus107.

By contrast, C-type lectins can have detrimental effects during virus infection. The recognition of HIV by DC-SIGN, for example, leads to virus uptake and productive infection in DCs, and subsequent trans-infection of CD4+ T cells104,108. Viral targeting of DC-SIGN also negatively affects several key cellular functions, including DC maturation, signalling induced through the TLRs, and activation of RIG-I-like receptors109. MMR is another C-type lectin that is involved in HIV binding and transmission, but has also been implicated in the recognition of many other viruses including, for example, dengue virus, influenza virus and hepatitis B virus108. The recognition of dengue, influenza and Ebola viruses by activating C-type lectins — such as DAP12-coupled CLEC5A and liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin; also known as CLEC4G) — induces damaging pro-inflammatory responses that contribute significantly to the pathology of these infections110-112. CLEC5A has also been implicated in dengue virus-induced osteoclast activation and alterations in bone homeostasis113. Polymorphisms of DC-SIGN, and other C-type lectins, are associated with alterations in viral disease susceptibility and outcome in humans114.

***[H3] Immunity to parasites***. Parasites including protozoa, nematodes and helminths possess numerous glycoconjugate structures that are capable of modulating innate and adaptive immune functions, most notably driving TH2 cell polarization115. Several well characterized C-type lectins have been implicated in these activities, including MBL, DC-SIGN and MMR, which can recognise a broad range of parasites, including *Leishmania* spp., *Trypanosoma cruzi* and *Schistosoma mansoni*115. In particular, polymorphisms influencing serum MBL levels have been linked to alterations in disease susceptibility to several parasites in humans116. However, our understanding of the role of C-type lectins in immunity to these pathogens is still relatively poor as the majority of experiments have been carried out *in vitro* and/or using isolated parasite glycoconjugates, such as *Schistosoma* egg antigen (SEA). The limited studies of infections in knockout mice have largely failed to establish a clear role for the most well-characterised C-type lectins *in vivo*, and evidence is now emerging that other C-type lectins are involved. Recognition of parasite glycoconjugates by MGL and SP-D, for example, were recently found to have an essential role in immunity by enhancing macrophage activation and parasite killing during infection with *T. cruzi* and *Nippostrongylus brasiliensis*, respectively117,118. Conversely, *Leishmania major* was shown to be able to evade immune responses *in vivo* by targeting mincle and inducing a novel inhibitory signalling pathway involving SHP1 recruitment to the Fcγ chain that impaired DC activation and the development of protective adaptive immunity69.

**[H1] C-type lectins in autoimmunity and inflammatory diseases**

C-type lectins are increasingly being recognised to have a key role in the control of immunological tolerance that is responsible for preventing autoimmune disease, and their functions have been implicated at all stages of disease progression through their ability to recognise endogenous and exogenous ligands, regulate cellular and inflammatory responses, and control adaptive immunity (FIG. 4). In fact many C-type lectins that function as PRRs, such as CLEC5A and mincle, also recognise DAMPs, thereby promoting inflammatory responses that can contribute to the pathology of these diseases (see also the discussion of cell death, above). C-type lectins also influence crucial aspects of B and T cell development; for example, the expression of CD69 is required for the development of functional Treg cells9, and LOX1 signalling in both DCs and B cells is required to induce B cell differentiation into class-switched plasmablasts54. In this section, we cover the most recent insights involving the role of C-type lectins in the major autoimmune diseases. Their roles in inflammatory bowel disease have been discussed above in the context of antimicrobial immunity.

***[H3] Arthritis***. There is considerable evidence from both mouse models and human studies that soluble and membrane-bound C-type lectins are involved in various arthropathies, including rheumatoid arthritis and osteoarthritis. In fact, polymorphisms of dectin 2 and DC-SIGN are thought to underlie, at least in part, the three-fold difference in gender susceptibility to rheumatoid arthritis, although the mechanisms behind this effect are unclear119. One of the most well-studied soluble C-type lectins in arthritis is the proteoglycan aggrecan, which is a major component of articular cartilage and is associated with the pathogenesis of both rheumatoid arthritis and osteoarthritis. Immunization of mice with aggrecan can induce chronic inflammatory arthritis, and several immunodominant epitopes within this molecule have been defined that can drive the induction of autoreactive T cells120. Notably, under inflammatory conditions, aggrecan is degraded by ADAMTS metalloproteinases and can become citrullinated; antibody and T cell reactivity to citrullinated aggrecan peptides are present in patients with rheumatoid arthritis and are thought to be causally related to pathology121. Polymorphisms influencing serum levels and activity of another soluble C-type lectin, MBL, have also been suggested to be involved in the pathogenesis of arthritis, but this has not been supported by a recent meta-analysis or in murine models122.

The pathogenesis of arthritis is regulated, at least in part, by the inhibitory activities of membrane-bound C-type lectins, including DCIR and MICL. For example, polymorphisms of DCIR in humans are associated with susceptibility to rheumatoid arthritis123, and mice lacking this receptor show aberrant DC proliferation and differentiation that leads to the spontaneous development of autoimmune sialadenitis and enthesitis, as well as increased pathology during collagen-induced arthritis124. Moreover, the ability of DCIR to regulate the differentiation of IFNγ-producing T cells is required for maintenance of bone homeostasis, as IFNγ was found to have chondrogenic and osteoblastogenic activity125. Loss of MICL also leads to exacerbated inflammation during collagen-specific antibody-induced arthritis in mice, as a result of aberrant myeloid cell activation, although the underlying mechanisms driving pathology are unclear126. Although polymorphisms of MICL are not directly associated with rheumatoid arthritis, a subset of patients possess MICL-specific autoantibodies, which are able to worsen disease when modelled in mice126.

The proinflammatory activities of activating C-type lectins can also exacerbate the pathology of arthritic disease. The inflammatory activities of CLEC5A and LOX1, including the production of pro-inflammatory cytokines and reactive oxygen species, promote joint damage, and loss or inhibition of these receptors is protective in murine models of rheumatoid arthritis and osteoarthritis, respectively127,128. In humans, the expression levels of both receptors positively correlate with disease severity129,130. Inhibition of NKG2D is similarly beneficial in murine models, presumably through its effect on IL-17 levels and cytotoxic effector functions (see above)131. Polymorphisms of NKG2D and its ligands have been associated with alterations in susceptibility and severity of rheumatoid arthritis in humans132.

***[H3] Type 1 diabetes***. CLEC16A is a membrane-associated endosomal protein that has been identified from genome-wide association studies **[G]** (GWAS) as a disease susceptibility gene for multiple autoimmune diseases. It has been mostly studied in the context of type 1 diabetes. CLEC16A interacts with the E3 ubiquitin ligase NRDP1 (also known as RNF41), which regulates mitophagy through the NRDP1–parkin pathway, and loss of this C-type lectin was proposed to impact mitochondrial function in pancreatic β cells133. However, in a more recent study, the effects of CLEC16A were attributed to changes in thymic epithelial cell autophagy and its impact on thymocyte selection, which might explain the broad effects of variation in this C-type lectin in different types of autoimmunity134. Variants of CLEC16A have also been associated with diseases including common variable immune deficiency disorder135 and selective immunoglobulin A deficiency136, which suggests that this molecule has a role in B cell function and/or development.

The alterations in glucose metabolism that occur during type 1 diabetes can influence the inflammatory activities of C-type lectins, such as LOX1 and MBL through mechanisms that are still unclear, but may involve the generation of agonistic receptor ligands, including advanced glycation end-products137,138. Expression levels of LOX1 and MBL are key risk factors for the development of diabetic complications, including pulmonary fibrosis139 and nephropathy, respectively. There are limited reports implicating other C-type lectins in the pathogenesis of type 1 diabetes, including DC-SIGN, CD93 and REG proteins, but their precise involvement is still unclear. C-type lectins also offer therapeutic opportunities in type 1 diabetes (BOX 2); for example, β-glucan stimulation of dectin 1 responses triggers protective innate immune-mediated modulation of autoreactive T cell responses140.

***[H3] Atherosclerosis***. LOX1 is a receptor for modified lipoproteins, particularly oxidized low density lipoprotein (oxLDL), that contributes significantly to the development of atherosclerosis and other cardiovascular diseases. LOX1 is upregulated on vascular endothelial cells under inflammatory conditions, and this C-type lectin receptor induces several cellular responses, including the production of reactive oxygen species and proinflammatory cytokines, apoptosis and cholesterol uptake, that contribute to atherogenic events such as endothelial dysfunction, foam cell and plaque formation, vascular smooth muscle cell proliferation, leukocyte recruitment and thrombogenesis141. Loss of LOX1 is protective in mouse models and several polymorphisms and alternative splice variants of this receptor in humans are associated with either promotion or protection from disease141,142. Given its importance in cardiovascular disease, there is much interest in developing inhibitors of this receptor for therapeutic use143 (BOX 2). Interestingly, statins, which are used clinically to reduce cholesterol biosynthesis, are also able to disrupt LOX1-mediated binding and internalization of oxLDL144.

Other C-type lectins involved in the pathogenesis of atherosclerosis include versican, SP-D, DNGR1 and mincle. The proteoglycan versican is highly upregulated in atherosclerotic lesions and is thought to have a key role in the retention of lipoproteins to vessel walls, leukocyte adhesion, vascular smooth muscle cell proliferation and thrombosis145. SP-D, which can be produced by vascular endothelial cells, is also involved in vascular lipid deposition, and loss of this receptor is protective in mouse models of disease 146, in part by reducing both systemic inflammatory responses and the local accumulation and proliferation of macrophages147. In humans, serum levels of and polymorphisms in SP-D correlate with the severity of cardiovascular disease148. In mouse models, DNGR1 has been implicated in promoting inflammation during the development of atherosclerosis, by downregulating the production of IL-10149. Mincle, which triggers inflammatory responses upon recognition of necrotic cells or cholesterol crystals150, was shown to promote a proatherogenic macrophage phenotype by inducing a SYK-dependent stress response in the endoplasmic reticulum that resulted in macrophage proliferation and induction of proinflammatory mediators151.

***[H3] Allergy***. Several C-type lectins, including dectin 1, dectin 2, mincle, DC-SIGN, MBL, MMR, DCIRs, SP-A and SP-D, have been implicated in the pathogenesis of allergy and other inflammatory disorders152. Recent data, for example, have shown that the ability of dectin 1 to recognise fungi and trigger innate inflammatory and TH17 cell responses contributes to the development of hypersensitivity pneumonitis153. Moreover, dectin 1 is involved in the induction of both eosinophilic and neutrophilic responses, as well as TH2 and TH17 cell differentiation, during fungal and house dust mite (HDM)-mediated allergic inflammation154. In fact, polymorphisms of dectin 1, MBL and SP-D are associated with susceptibility to severe asthma in humans155,156. Attention has focused on the unusual ability of dectin 2 to induce a SYK- and PKCδ-dependent signalling pathway, in response to HDM, which results in the production of cysteinyl leukotrienes and other proinflammatory mediators, as well as IL-33, promoting allergic TH2 and TH17 cell responses58. C-type lectins such as DC-SIGN and MMR can also recognize common allergens, including BG-60 (pollen), Arah1 (peanut) and Derp2 (HDM), as well as others in allergenic foods157. This modulates subsequent T cell responses, in part through downregulation of the indolamine-2,3-dioxygenase pathway and the production of cytokines such as IL-12p70, which promotes the development of TH2 cell responses158. Mincle was shown to recognize cholesterol sulfate, which is present at high concentrations in epithelial barriers, leading to the induction of proinflammatory mediators that exacerbate allergic skin responses to this ligand upon epithelial damage. In mice, REG3γ was recently found to be induced by IL-22 and to have an important role in regulating epithelial immune responses during allergic inflammation although the underlying mechanisms are incompletely understood159.

Versican facilitates leukocyte recruitment during allergic responses by modifying the ECM, as described above12. Although there are only correlative data regarding levels of versican and its impact on allergic disease in humans, versican deficiency in mouse models attenuated leukocyte recruitment, which markedly reduced pathology of the disease12. Leukocytes associated with allergy, including basophils and eosinophils, also express C-type lectins that influence their recognition of and response to allergens160. Notably, a predominant constituent of eosinophil secondary granules is the C-type lectin eosinophil major basic protein (also known as EMBP), which disrupts lipid membranes and is toxic to mammalian cells, and which can induce epithelial cell damage, bronchoconstriction, airway hyperreactivity and histamine release from mast cells and basophils161.

***[H3] Other autoimmune diseases***. C-type lectins have been implicated in a range of other autoimmune diseases, including psoriasis, multiple sclerosis, uveitis and systemic lupus erythematosus (SLE). For example, CD69 regulates the pathogenesis of psoriasis by modulating cell surface expression of the aromatic-amino-acid transporter LAT1–CD98 on γδ T cells, which controls the uptake of L-tryptophan and subsequent aryl-hydrocarbon receptor-dependent secretion of IL-22162, a key cytokine that has been linked to pathology of the disease. The pathogenesis of multiple sclerosis involves several C-type lectins, including the inhibitory receptor DCIR2, which functions to suppress autoimmunity by restricting the activation and induction of inflammatory responses by CD8α– cDCs, thereby downregulating subsequent T cell priming163. Similarly, in the development of SLE, CD72 inhibits B cell responses upon recognition of self antigen in the form of Sm ribonucleoproteins, limiting the production of pathogenic autoantibodies164. By contrast, in murine models of autoimmune uveitis, mincle and dectin 1 were shown to drive proinflammatory TH17 cell responses that promote development of the disease, although it is unclear what ligands are being recognised by these receptors in these autoimmune models165,166.

**[H1] Concluding remarks**

C-type lectins are an extraordinary superfamily of proteins that recognise a wide diversity of ligands and that are required for numerous essential functions in mammals. In this Review, we have summarized the most recent discoveries involving these molecules themed according to their physiological functions. The rapid expansion of our knowledge about the roles and functions of C-type lectins over the past few years has greatly increased our understanding of the mechanisms underlying development and homeostasis, as well as resistance and susceptibility to infectious and non-infectious diseases. This knowledge presents exciting opportunities for novel diagnostics, adjuvants and vaccination strategies, as well as new targets and strategies for the treatment and prevention of disease.

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**DATABASES**

UniProtKB: http://www.uniprot.org

**FURTHER INFORMATION**

Imperial College London C-type Lectins website: http://www.imperial.ac.uk/research/animallectins/ctld/classes/C-type1.html

**SUPPLEMENTARY INFORMATION**

See online article: S1 (table)

All links are active in the online pdf

**Box 1: Intracellular signalling mediated by C-type lectins**

Transmembrane C-type lectin receptors (CLRs) can trigger signalling pathways that broadly result in the activation or inhibition of cellular functions. Best studied are those receptors that induce activation pathways through immunoreceptor tyrosine-based activation motifs (ITAMs). Such ITAMs can either be an integral component of the CLR cytoplasmic tail (for example, in dectin 1 and DNGR1) or can require the use of signalling adaptors, such as the Fc receptor γ-chain (FcRγ; for dectin 2, MCL and mincle) or DAP10 (DAP12 in mice; for NKG2D, CLEC5A and LSECtin). In myeloid cells, these ITAM domains facilitate the recruitment of SYK kinase (or ZAP70 in T cells, used by the T cell receptor), which induces a downstream signalling pathway involving the CARD9–BCL10–MALT1 complex (reviewed in REF.53) that results primarily in the induction of nuclear factor-κB (NF-κB)-dependent proinflammatory responses. Receptors such as DC-SIGN associate with the adaptor lymphocyte specific protein 1 (LSP1) and can recruit the RAF1 signalosome, inducing a poorly defined SYK-independent pathway that enhances signalling from other receptors, including the Toll-like receptors (reviewed in REF.53). Notably, activation of this pathway and recruitment of the RAF1 signalosome can be dependent on the nature of the carbohydrate ligands recognised, which influences the nature of the inflammatory response and subsequent adaptive immunity53. For instance, binding of mannose-expressing pathogens such as *M. tuberculosis* by DC-SIGN requires the recruitment of the upstream effectors LARG and RhoA for activation of the RAF1 signalosome. Subsequent downstream RAF1 signalling results in phosphorylation and acetylation of the p65 subunit of NF- κB thereby enhancing pro-inflammatory responses. Phosphorylated p65 may also interact with RelB to form a transcriptionally inactive dimer during Dectin-1 triggered non-canonical NF- κB signalling. A few CLRs (for example, NKG2D and CLEC5A) associate with the adaptor protein DAP10, which induces signalling through p85 phosphatidylinositol 3-kinase (PI3K) and a GRB2–VAV1 signalling complex that also requires ubiquitin-dependent endocytosis for activation of NK cell effector functions via ERK1/2, primarily providing co-stimulation to signals induced by other receptors167. By contrast, inhibitory receptors such as MICL recruit tyrosine and inositol phosphatases, including SHIP1 and SHP1, to negatively regulate the signalling pathways induced by other receptors, and they are generally thought to suppress the inflammatory pathways induced by activating receptors168. The cytoplasmic tails of many CLRs (including CD93, L-selectin, layilin and thrombomodulin) can interact directly with the actin cytoskeleton through ezrin, radixin and moesin (ERM) proteins, facilitating its reorganization for functions such as phagocytosis, cellular adhesion and migration 3,169,170. Polycystic kidney disease 1 (PKD1) comprises part of a calcium channel and may function as an atypical G-protein-coupled receptor, regulating several intracellular signalling pathways, including mechanistic target of rapamycin (mTOR) through mTOR complex 1 (mTORC1) and WNT/β-catenin signalling, that are required for its functioning in renal tubular morphogenesis 171. PKD1 regulates canonical WNT/β-catenin signalling through cleavage of its C-terminal tail (CTT) which reduces the ability of β-catenin to promote T-cell factor (TCF) dependent transcription of WNT target genes. The signalling pathways mediated by other CLRs such as MMR or DEC205 remain unknown. CTT, PKD1 C-terminal tail; TCF, T cell factor.

**Box 2: Therapeutic potential of C-type lectin receptors**

The exploitation of C-type lectins and their signalling pathways offers considerable promise for the future development of novel diagnostics and therapeutic approaches. (**a**) C-type lectins can function as useful biomarkers for disease; for example, serum levels of mannose-binding lectin (MBL) can be used to predict autoimmune and infectious disease susceptibility. (**b**) C-type lectins can enhance the efficacy of vaccines, through approaches such as antigen-coupled antibodies targeting CLRs (for example, DEC205 or CLEC9A172) on dendritic cells (DCs) or through the use of synthetic CLR ligands, such as the mincle agonist trehalose dibehenate (TDB). (**c**–**f**) Stimulation with C-type lectins can induce innate and adaptive immune responses that are protective for both infectious and non-infectious diseases. (**c**) C-type lectin ligands such as β-glucan can induce trained ‘innate’ immunity173, whereby long-term immune protection is promoted by epigenetic changes in monocytes and macrophages.(**d**) β-glucan treatment has been shown to induce protective responses during oncogenesis by stimulating the apoptosis of immunosuppressive neutrophilic myeloid-derived suppressor cells (MDSCs) and the conversion of monocytic MDSCs to potent antigen-presenting cells (APCs), enhancing anti-tumour CD4+ and CD8+ T cell-mediated immune responses. (**e**)Conversely, antagonists of C-type lectins could prove beneficial, such as antagonists of LOX1 to prevent the uptake of oxidised-low density lipoprotein (oxLDL) by vascular endothelial cells, which is a key event in the initiation of atherosclerotic plaques. (**f**)Inhibition of C-type lectin-induced signalling pathways can also induce protective responses. For example, inhibitors of JNK1 downstream of dectin 1 can improve the dectin 1-induced immune response to *Candida albicans* through nuclear factor of activated T cells (NFAT).

**Figure 1: Representative C-type lectin structures**

Cartoon representation of the structures of the major soluble and membrane-bound C-type lectins described in this Review. C-type lectins, which have at least one C-type lectin-like domain (CLTD), are divided into 17 subgroups on the basis of their phylogeny and domain organisation. The names of the C-type lectins of interest are shown as are the group numbers and family names (both in parenthesis) to which they belong. See also Supplementary information S1 (table). The assignation of each protein to a specific C-type lectin family is as described by the Imperial College London C-type Lectins website [<http://www.imperial.ac.uk/research/animallectins/ctld/mammals/humanvmousedata.html>]. The major protein domains, in addition to the CTLD, for each C-type lectin are also indicated and were annotated as in the UniProtKB database [<http://www.uniprot.org/uniprot/>]: CUB, complement C1r/C1s, Uegf, Bmp1; EGF-like, epidermal growth factor-like; GAG, glycosaminoglycan; GPS, G-protein-coupled receptor proteolytic site; LDL, low-density lipoprotein; PKD, polycystic kidney disease; PSI, plexin–semaphorin–integrin; REJ, receptor for egg jelly; WSC, cell wall integrity and stress response components. Not drawn to scale. MBL, mannose-binding lectin; MMR, macrophage mannose receptor; SP-D, surfactant protein D.

**Figure 2: Role of C-type lectins in cancer**

C-type lectins both promote and suppress antitumour immune responses. In natural killer (NK) cells, C-type lectins facilitate the recognition of cellular transformation and prevent the attack of healthy cells, through the interaction between MHC class I molecules and C-type lectins such as LY49 (in mice), which trigger inhibitory signalling pathways. Alterations in the levels of MHC class I expression or the induction of MHC class-I like molecules, such as MICA, by cellular stress, leads to the activation of C-type lectins such as NKG2D, which induces the cytotoxic activities of NK cells. C-type lectin receptors expressed by myeloid cells, such as dectin 1, dectin 2 and MCL, also mediate protective responses by recognising cancer-associated carbohydrate antigens and facilitating cancer cell uptake and clearance, the activation of NK cells and the suppression of damaging proinflammatory responses. However, recognition of tumour-associated carbohydrates, as well as tumour-associated components such as galectin 9 and SAP130 (spliceosome-associated protein 130), by C-type lectins including dectin 1, mincle, MGL and DC-SIGN can suppress protective responses. Moreover, protective antitumour responses can also be suppressed following the release of lactate dehydrogenase (LDH) by cancer cells, which induces expression of NKG2D ligands on myeloid cells and results in the downregulation of NKG2D on NK cells. The metastasis of cancer cells is enhanced by expression of C-type lectins, such as L-selectin which facilitates adherence to endothelium, and of C-type lectin ligands, such as podoplanin, which induces CLEC2-mediated platelet aggregation. Platelet aggregation provides protection from leukocytes such as NK cells, as well as shear stress.

**Figure 3: Cellular functions of transmembrane C-type lectins in antimicrobial immunity**

**a |** Recognition of extracellular pathogens by transmembrane C-type lectin receptors (CLRs) in myeloid cells induces intracellular signalling pathways (BOX 1) that result in numerous cellular responses that are crucial for controlling infection. Many CLRs, such as dectin 1, mediate the uptake of pathogens through phagocytosis, inducing antimicrobial effector mechanisms such as the NADPH oxidase-mediated respiratory burst. Recognition of pathogens by CLRs can also induce arachidonic acid metabolism and the production of immunomodulatory lipids, such as the eicosanoids. CLRs can induce the transcription of numerous cytokines and chemokines, which are generally proinflammatory such as tumour necrosis factor (TNF), although anti-inflammatory cytokines such as IL-10 are also produced. CLRs also induce the production of pro-IL-1β, and its processing to its active form, either directly by the Caspase-8 inflammasome, or indirectly by the Caspase-1-linked NLRC4 and NLRP3 inflammasomes. In neutrophils, CLR-mediated phagocytosis of pathogens and induction of intracellular reactive oxygen species by NADPH limits the production of IL-1β and results in the targeting of neutrophil elastase to the phagolysosome. For large pathogens that cannot be phagocytosed, IL-1β production is uninhibited, leading to further neutrophil recruitment, and neutrophil elastase translocates to the nucleus and induces NETosis. In dendritic cells, CLR-mediated uptake and killing of pathogens leads to the induction of costimulatory molecules and enhanced antigen presentation to CD4+ T cells. CLRs such as DNGR1 can also facilitate the cross-presentation of antigens to CD8+ T cells. Notably, the cytokines induced by CLRs, such as IL-12, IL-23, IL-1β and IL-6, direct the polarization of adaptive immunity. Dashed lines indicate incompletely understood mechanisms. **b |** In lymphocytes, including γδ T cells and human B cells, the direct recognition of pathogens by CLRs such as Dectin 1 induces the production of proinflammatory cytokines, including IL-8, tumour necrosis factor (TNF) and IL-6, as well as those normally associated with adaptive immunity, such as interferon-γ (IFNγ) and IL-17. CLRs such as NKG2D expressed by cytotoxic lymphocytes, including natural killer cells and cytotoxic T lymphocytes, have a key role during viral infection by sensing alterations in the expression of MHC class I or MHC class I-like ligands on infected target cells. Expression of these ligands induces lymphocyte inflammatory responses and cytotoxic effector mechanisms, including expression of FAS ligand (FASL; also known as CD95L) and induction and exocytosis of cytotoxic granules containing perforin and granzyme, which together induce target cell apoptosis.

**Figure 4: C-type lectins in autoimmunity**

C-type lectins can both enhance and delay the progression of autoimmune disease. In a genetically predisposed individual, the recognition of C-type lectin receptor (CLR) ligands or self antigens by soluble collectins (such as MBL and SP-D) and transmembrane C-type lectins induces innate immune activation and self-antigen presentation to autoreactive adaptive immune cells. If immunological tolerance mechanisms fail, autoreactive B and T cells proliferate and differentiate into effector cells that are responsible for the autoimmune pathology. Inhibitory C-type lectins such as DCIR and MICL regulate this activation pathway and autoantibodies targeting these C-type lectins may enhance disease. C-type lectins are also involved in the control of B and T cell development. For example, CLEC16A modulates thymic epithelial cell autophagy and subsequent antigen presentation to thymocytes undergoing selection in the thymus. Altered expression of CLEC16A has been associated with multiple autoimmune diseases.

**Glossary**

**Proteoglycans**

Proteins that are heavily glycosylated, normally with one or more covalently attached glycosaminoglycans. They are found in the extracellular matrix, in connective tissue and on the surface of cells.

**Autosomal dominant polycystic kidney disease**

One of the most common monogenic diseases found in humans, characterised by structurally abnormal renal tubules that form fluid-filled cysts.

**Fibroblastic reticular cells**

(FRCs). Myofibroblast stromal cells of mesenchymal origin found in lymphoid tissues which express the CLEC-2 ligand podoplanin, and which create a three dimensional network facilitating antigen transport and leukocyte migration.

**Myeloid-derived suppressor cells**

(MDSCs). A heterogeneous population of cells of myeloid origin that have the ability to suppress T cell responses in multiple diseases. MDSCs can be further divided into monocytic MDSCs and neutrophilic MDSCs.

**Pattern-recognition receptors**

(PRRs). Receptors that bind to conserved molecular patterns normally found in pathogens (pathogen-associated molecular patterns (PAMPS)), but also to structures associated with cellular damage (damage-associated molecular patterns (DAMPs)). Examples of PAMPs include β-glucans and lipopolysaccharide. Examples of DAMPs include F-actin and SAP130.

**Neutrophil extracellular traps**

(NETs). Extracellular structures consisting of DNA, hydrolytic enzymes and other antimicrobial components that are produced following the induction of a defined cell death programme in neutrophils. NETs, and similar structures produced by other cell types, trap and kill microorganisms extracellularly.

**Adjuvants**

In the immunological context, adjuvants are compounds that potentiate or boost the immunogenicity of an antigen. Adjuvants are required to improve the efficacy of vaccines, as they stimulate innate immune responses that promote the development of adaptive immunity to the vaccine antigens.

**Autophagy**

An intracellular ‘uptake’ mechanism that induces the membrane enclosure of intracellular components and their targeting to the lysosomal pathway for degradation.

**Cytotoxic T lymphocyte**

(CTL). CTLs are CD8+ T cells that can kill infected, transformed or damaged cells. CTLs recognise cellular antigens that are presented in the context of MHC class I molecules, which can trigger their cytotoxic activities either directly, through the release of perforin, granzymes and granulysin that enter and kill the target cells, or indirectly, through expression of FAS ligand, which binds to FAS on the surface of target cells, inducing a death-associated intracellular signalling pathway.

**Genome-wide association studies**

(GWAS). The objective of a GWAS is to determine if a genetic variant (normally a single-nucleotide polymorphism) found within a population is associated with a trait of interest, such as a specific disease.

**Subject categories**

Biological sciences / Immunology / Tumour immunology

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Biological sciences / Immunology / Cell death and immune response

[URI /631/250/1933]

Biological sciences / Immunology / Antimicrobial responses

[URI /631/250/2499]

Biological sciences / Immunology / Autoimmunity

[URI /631/250/38]

Biological sciences / Immunology / Infectious diseases

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Recently discovered roles for C-type lectins in development, homeostasis, cell death, cancer and autoimmune and inflammatory diseases extend the functions of this superfamily beyond their well-recognised involvement in antimicrobial responses.