C-type lectins in immunity and homeostasis

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Abstract | The C-type lectins are a superfamily of proteins that recognize 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 recognized 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 organization[1] (FIG. 1; Supplementary Table 1; and see also the Imperial College London C-type Lectins website). These molecules were originally named for their ability to bind to carbohydrates in a Ca^{2+}-dependent manner through conserved residues within the CTLD; these include the EPN (Glu–Pro–Asn) and QPD (Gln–Pro–Asp) motifs, which confer specificity for mannose-type and galactose-type carbohydrates, respectively[1,2]. However, the CTLDs of many C-type lectins lack the components required for Ca^{2+}-dependent carbohydrate recognition and can recognize a broader repertoire of ligands including proteins, lipids and even inorganic molecules, such as ice[1,2].

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 because of their ability to recognize self (endogenous) and non-self (exogenous) ligands. In fact, many C-type lectins can recognize both classes of ligand and are involved in numerous 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, CD93 (also known as C1QR1) and thrombomodulin) 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.

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 Table 1). 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 tissues[3,4]. 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-specific 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

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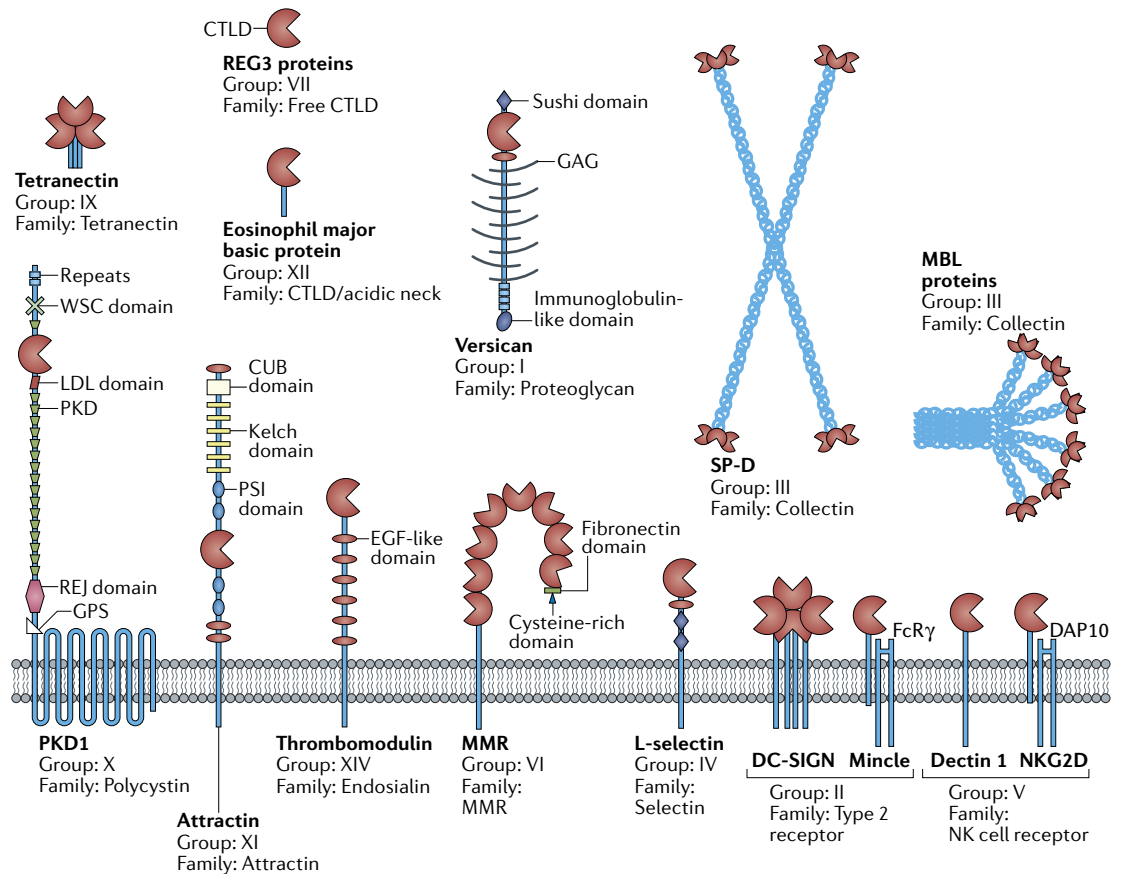
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Fig. 1 | **Representative C-type lectin structures.** A cartoon representation of the structures of the major soluble and membrane-bound C-type lectins described in this Review. C-type lectins, which have at least one C-type lectin-like domain (CLTD), are divided into 17 subgroups on the basis of their phylogeny and domain organization. The names of the C-type lectins of interest are shown, as are the group numbers and family names to which they belong. See also Supplementary Table 1. The assignation of each protein to a specific C-type lectin family is as described by the Imperial College London C-type Lectins website. The major protein domains, in addition to the CTLD, for each C-type lectin are also indicated and are annotated as they are found in the UniProtKB database. The image is not drawn to scale. CUB, complement C1r/C1s, UEGF, BMP1; EGF, epidermal growth factor; FcRγ, Fc receptor γ-chain; GAG, glycosaminoglycan; GPS, G protein-coupled receptor proteolytic site; LDL, low-density lipoprotein; MBL, mannose-binding lectin; MMR, macrophage mannose receptor; PKD, polycystic kidney disease; PSI, plexin–semaphorin–integrin; REJ, receptor for egg jelly; SP-D, surfactant protein D; WSC, cell wall integrity and stress response components.

to identify human CD141+BDCA3+ conventional type 1 DCs (cDC1s)[5–7]. The expression of other C-type lectins is tightly regulated, and they are induced only under particular conditions, such as inflammation[8]. These molecules can be useful as indicators of cellular state; for example, CD69 is rapidly expressed upon cell stimulation and is widely used as a marker to indicate the activation state of lymphocytes and NK cells[9]. There is also species specificity in the expression profiles of some C-type lectins (Supplementary Table 1). 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 humans[10].
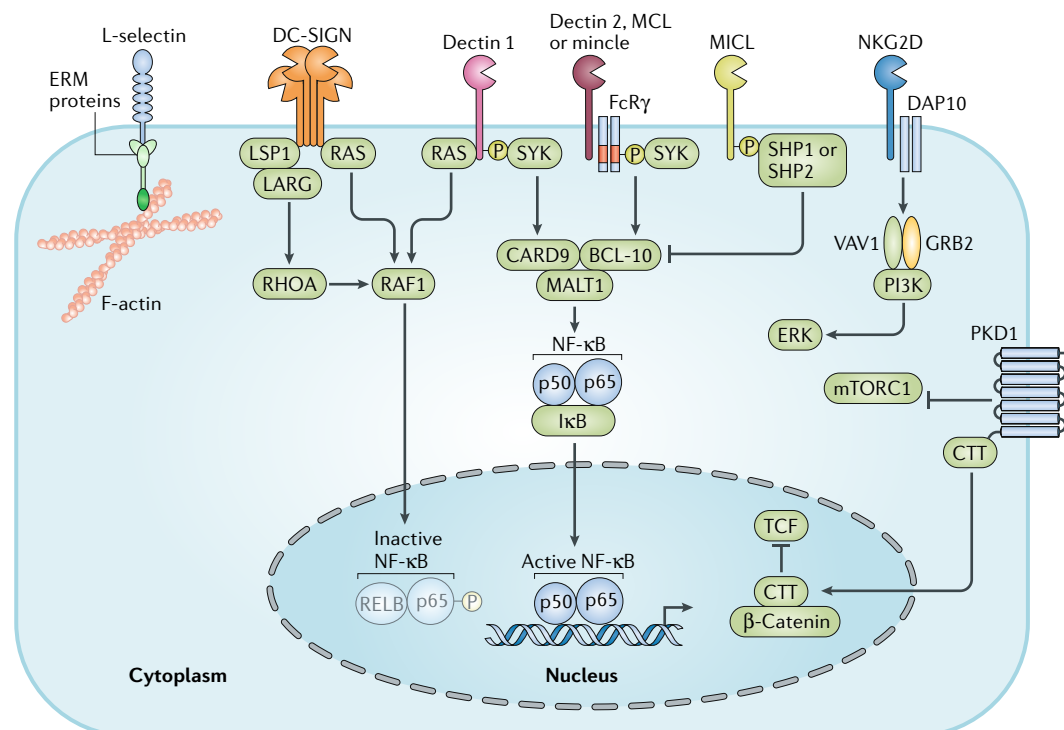
Homeostasis, cell death and cancer

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 characterized, and our understanding of their contributions and underlying mechanisms remains incomplete. In this section, we divide 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.

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, including surfactant protein A (SP-A; also

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). These ITAMs can either be an integral component of the CLR cytoplasmic tail (for example, in dectin 1 and dendritic cell, natural killer (NK) cell lectin group receptor 1 (DNGR1)) or can require the use of signalling adaptors, such as the Fc receptor γ-chain (FcRγ; for dectin 2, macrophage C-type lectin (MCL) and macrophage-inducible C-type lectin (mincle)) or DAP10 (DAP12 in mice; for NKG2D, CLEC5A and liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin)). In myeloid cells, these ITAMs facilitate the recruitment of SYK kinase (or tyrosine-protein kinase ZAP70 in T cells, which is used by the T cell receptor), which induces a downstream signalling pathway involving the caspase-recruitment domain protein 9 (CARD9)–B cell lymphoma/leukaemia 10 (BCL-10)–mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) complex (reviewed in REF.[53]). These signalling pathways result primarily in the induction of nuclear factor-κB (NF-κB)-dependent pro-inflammatory responses. Receptors such as DC-SIGN associate with the adaptor lymphocyte-specific protein 1 (LSP1) and can recruit the serine/threonine-protein kinase RAF1 signalosome, inducing a poorly defined SYK-independent pathway that increases 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 recognized, which influences the nature of the inflammatory response and subsequent adaptive immunity[53]. For example, binding of mannose-expressing pathogens such as *Mycobacterium tuberculosis* by DC-SIGN requires the recruitment of the upstream effectors leukaemia-associated RHO-GEF (LARG; also known as ARHGEF12) 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 increasing pro-inflammatory responses. Phosphorylated p65 may also interact with transcription factor 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 the p85 subunit of phosphoinositide 3-kinase (PI3K) and a growth factor receptor-bound protein 2 (GRB2)–VAV1 signalling complex that also requires ubiquitin-dependent endocytosis for the activation of NK cell effector functions through extracellular signal-regulated kinase 1 (ERK1; also known as MAPK3) and ERK2 (also known as MAPK1), primarily providing co-stimulation to signals induced by other receptors[167]. By contrast, inhibitory receptors such as myeloid inhibitory C-type lectin (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 receptors[168]. The cytoplasmic tails of many CLRs (including CD93, L-selectin, layilin and thrombomodulin) can interact 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) forms part of a Ca²⁺ 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 functions in renal tubular morphogenesis[171]. PKD1 regulates canonical WNT–β-catenin signalling through cleavage of its carboxy-terminal tail (CTT), which reduces the ability of β-catenin to promote T cell-specific transcription factor (TCF)-dependent transcription of WNT target genes. The signalling pathways mediated by other CLRs such as macrophage mannose receptor (MMR) or DEC205 remain unknown.

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 lining[11]. Other secreted C-type lectins constitute part of the ECM, such as the proteoglycans versican (VCAN), aggrecan 1 (AGC1) and FRAS1-related ECM 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 gradients[12]. Tetranectin (also known as CLEC3B), which is present in the serum at high concentrations, increases plasminogen activation by facilitating its association with tissue plasminogen activator. Furthermore, tetranectin can bind fibrin, heparin and other sulfated polysaccharides and is involved in osteogenesis, tissue remodelling and wound healing, although the underlying mechanisms involved are still unclear. Remarkably, mutations in the gene encoding this C-type lectin are associated with extreme longevity in humans[13]. 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 maintenance[14]. The transmembrane C-type lectin polycystic kidney disease 1 (PKD1) functions as a mechanosensor on primary cilia in a complex with the structurally unrelated Ca^{2+}-permeable cation channel PKD2, and mutations in the genes encoding PKD1 and PKD2 result in autosomal dominant polycystic kidney disease[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 development[16]. Although the underlying mechanisms are still unclear, recent evidence indicates that these functions are independent of the signalling activities of either protein[17,18]. Moreover, the interaction of CLEC2 on DCs with podoplanin-expressing fibroblastic reticular cells (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 response[19,20]. 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 endocytosis[21]), intravascular coagulation (for example, thrombomodulin binds thrombin and changes its substrate specificity for protein C[22]) and maintenance of haematopoietic stem cells (for example, CLEC2 regulates thrombopoietin production by megakaryocytes[23]), 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]).

Cell death. C-type lectins are involved in the sensing and removal of dead and dying cells, which are crucial processes for maintaining tissue and organ homeostasis. Soluble C-type lectins, such as the collectins — mannose-binding lectin 1 (MBL1) in mice and MBL2 in mice and humans (referred to here collectively as MBL), SP-A, SP-D and collectin kidney protein 1 (CL-K1; also known as collectin 11) — 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 oxidized 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 DNGR1 (REF.[29])), uric acid (which binds MICL[28]), and SAP130 and β-glucosylceramide (both of which are recognized by mincle[30]). 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 SHP2 (REFS[27,28,30]) (BOX 1). Inflammatory responses induced by mincle in response to DAMPs have been recently linked to alcoholic liver disease[31], hepatitis[32], obesity-induced adipose tissue fibrosis[33], ischaemia pathogenesis[34], cancer[35] and allergy[36]. 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 uptake[37,38]. The physiological role of both of these receptors is still largely unclear, although the cross-presentation activities mediated by DNGR1, which are induced through the SYK pathway[27], are required for protection against certain viral pathogens (described below).

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 suppression[39] (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 metastasis[40]. Expression of the homing receptor L-selectin facilitates lymphatic metastasis of cancer cells[4], whereas systemic downregulation of this C-type lectin on naive T cells, by tumour-induced
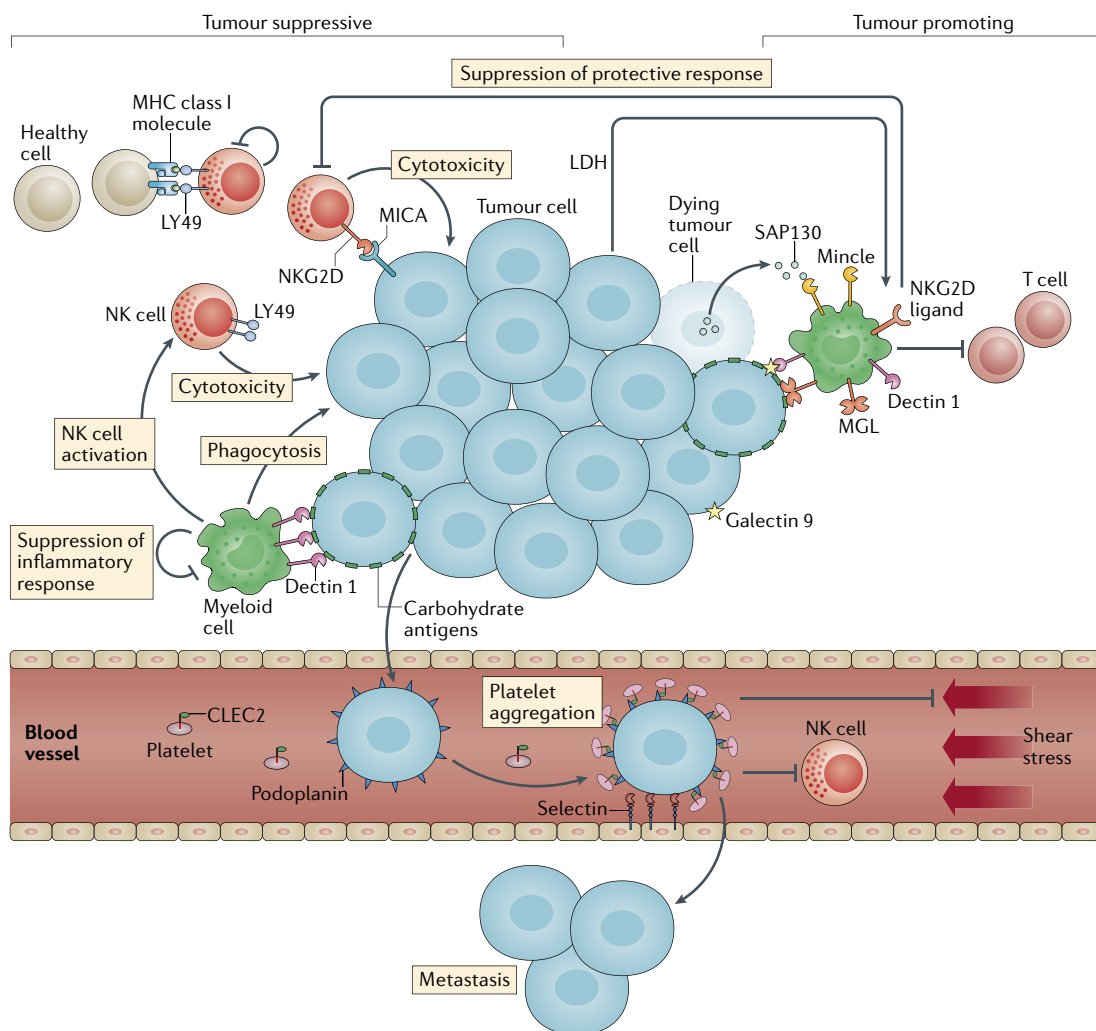
Fig. 2 | **Role of C-type lectins in cancer.** C-type lectins both promote and suppress antitumour immune responses. In natural killer (NK) cells, C-type lectins facilitate the recognition of cellular transformation and prevent the attack of healthy cells through the interaction between MHC class I molecules 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 macrophage C-type lectin (MCL), also mediate protective responses by recognizing cancer-associated carbohydrate antigens and facilitating cancer cell uptake and clearance, the activation of NK cells and the suppression of damaging pro-inflammatory 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, macrophage-inducible C-type lectin (mincle), macrophage galactose lectin (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 increased 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 protection from shear stress.

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.

myeloid-derived suppressor cells (MDSCs), disrupts T cell trafficking to secondary lymphoid tissues and the induction of a protective antitumour immune response[41]. 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, respectively[35,42]. 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 responses[39]. 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 antitumour 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' (REF.[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 the induction of inhibitory NK cell signalling are 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 recognizes 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 caused by events 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 pathways[44] (BOX 1). Tumour cells are thought to be able to evade these responses by shedding NKG2D ligands to desensitize NK cells, although recent evidence suggests that shedding ULBP1 can restore NK cell activation and protective immunity[45]. 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 responses[46].

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 suppress liver metastasis by facilitating the phagocytosis and clearance of cancer cells[47]. Dectin 1 is also protective during hepatocarcinogenesis by suppressing Toll-like receptor 4 (TLR4) signalling and inflammation[48]. Dectin 1 can recognize selected N-glycan structures on tumour cells, triggering interferon regulatory factor 5 (IRF5)-dependent responses in DCs or macrophages that activate the tumoricidal activity of NK cells[49]. 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

MDSCs[50] and by inducing antitumour IL-9-producing T cells[51]. Moreover, myeloid cell-expressed C-type lectins, including DEC205, DNGR1, MGL and MICL, have been explored as targets on DCs to promote antigen uptake and boost antitumour and other immune responses[52]. Aberrant expression patterns of these receptors in cancer can also function as diagnostic or prognostic markers of disease.

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) through their ability to recognize 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 CL-K1), 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). The ability of CLRs to direct the development of adaptive immunity (particularly, T helper 1 (T_H1) cell, T_H17 cell[53] and B cell[54] responses) has been of considerable interest because of the importance of these responses in the control of systemic and mucosal infections 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 important advances made with respect to the C-type lectins during the time frame of this Review have focused on this receptor.

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 responses[55] (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 pathways[56]. 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 (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-1β[57]. In general, the responses induced by CLRs are pro-inflammatory, 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,

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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 spliceosome-associated protein 130 (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.

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. 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 (see the figure, part **a**). C-type lectins can increase the effectiveness of vaccines through approaches such as antigen-coupled antibodies targeting C-type lectin receptors (CLRs) on dendritic cells (DCs) (for example, DEC205 or DNGR1 (REF.[172]) or through the use of synthetic CLR ligands, such as the macrophage-inducible C-type lectin (mincle) agonist trehalose dibehenate (TDB) (part **b**). Stimulation with C-type lectins can induce innate and adaptive immune responses that are protective for both infectious and non-infectious diseases (parts **c–f**). C-type lectin ligands such as β-glucan can induce 'trained' innate immunity[173], whereby long-term immune protection is promoted by epigenetic changes in monocytes and macrophages (part **c**). Treatment with β-glucan 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), which improves antitumour CD4^{+} and CD8^{+} T cell-mediated immune responses (part **d**). Conversely, there could be a beneficial role for antagonists of C-type lectins, such as the use of oxidized low-density lipoprotein receptor 1 (LOX1) antagonists to prevent the uptake of oxidized low-density lipoprotein (oxLDL) by vascular endothelial cells, which is a key event in the initiation of atherosclerotic plaques (part **e**). Inhibition of C-type lectin-induced signalling pathways can also induce protective responses (part **f**). For example, inhibitors of stress-activated protein kinase JNK1 (also known as MAPK8) that functions downstream of dectin 1 can improve the dectin 1-induced immune response to *Candida albicans* through activation of nuclear factor of activated T cells (NFAT).
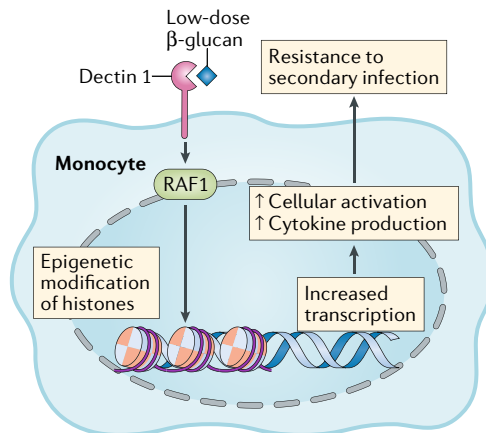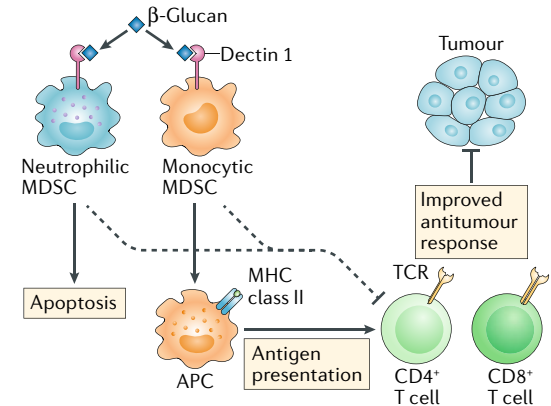
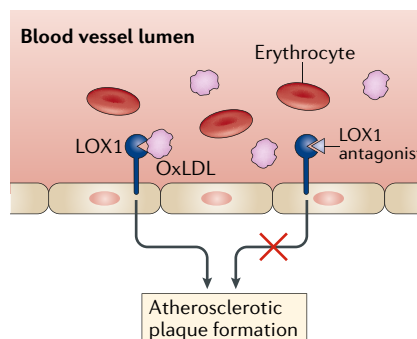**a** Biomarkers of disease
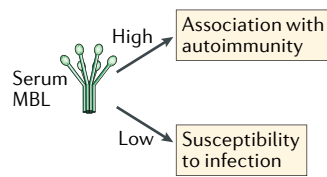
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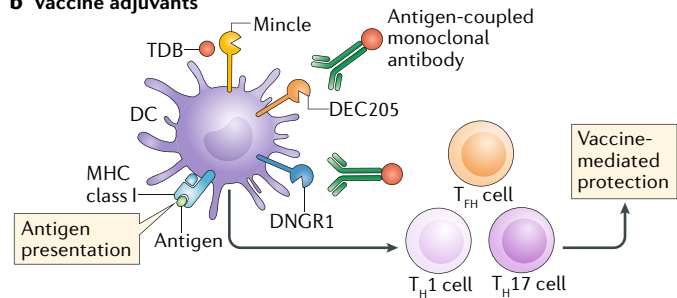
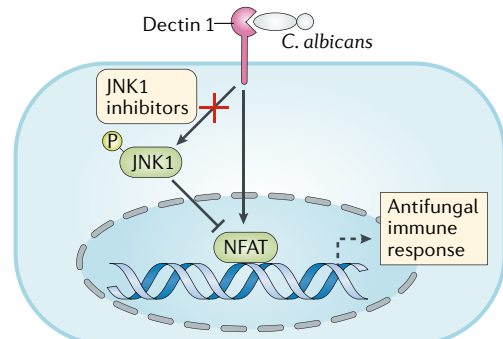**c** Induction of trained innate immunity

d Induction of antitumour response

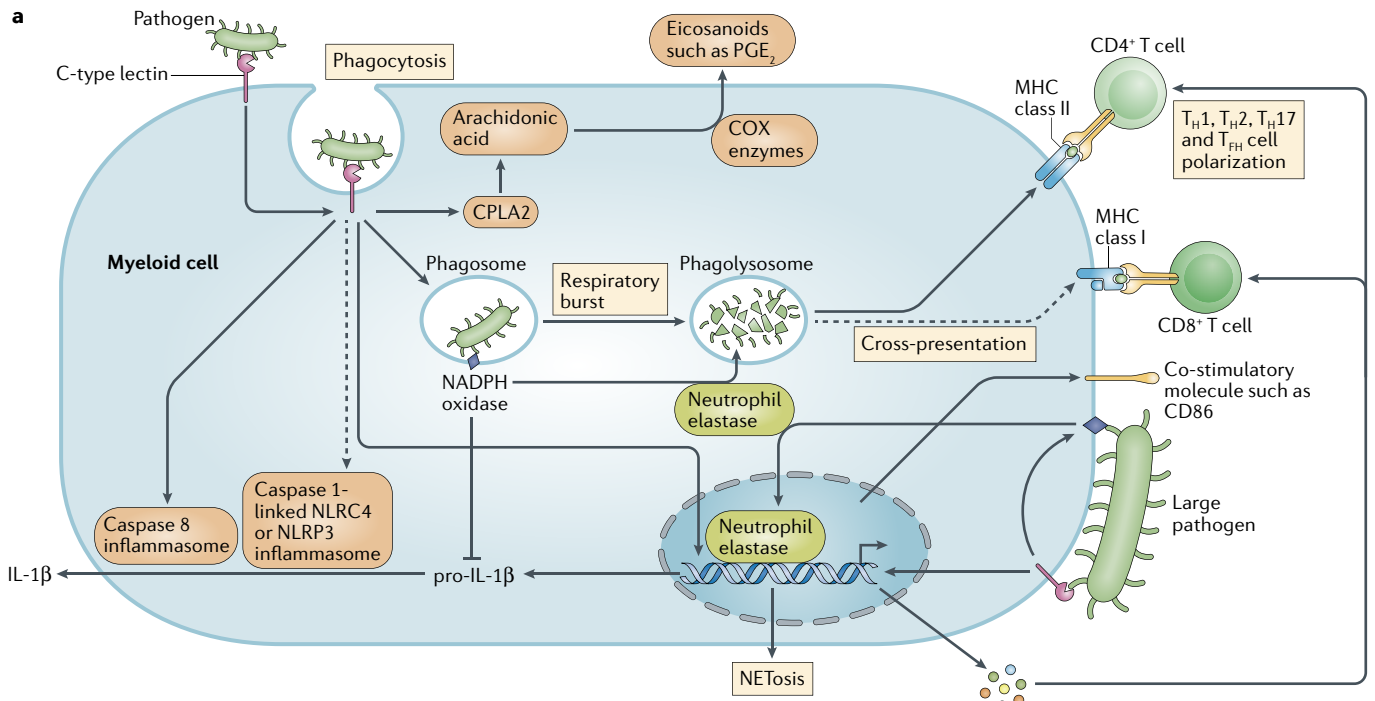**e** CLR antagonists

f Antifungal drug improvements

Fig. 3 | **Cellular functions of transmembrane C-type lectins in antimicrobial immunity.**
a | The 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 pro-inflammatory, 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 lead to the induction of co-stimulatory molecules and increased antigen presentation to CD4+ T cells. CLRs such as dendritic cell, natural killer cell lectin group receptor 1 (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 pro-inflammatory cytokines, including CXC-chemokine ligand 8 (CXCL8), 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 antigen ligand (FASL; also known as CD95L) and induction and exocytosis of cytotoxic granules containing perforin and granzyme, which together induce target cell apoptosis. COX, cyclooxygenase; CCL, CC-chemokine ligand; CPLA2, cytosolic phospholipase A2; PGE2, prostaglandin E2; TH, T helper.
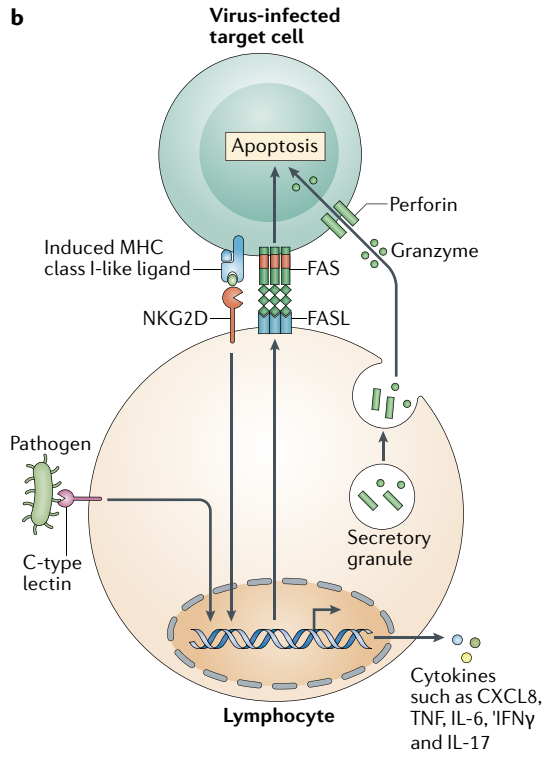
such as IL-10. In DCs, CLRs facilitate antigen presentation to CD4+ T cells and the cross-presentation of antigens to CD8+ T cells and direct the development of adaptive immunity (mainly TH1, TH17 and T

follicular helper (TFH) cell responses, although dectin 2 has also been shown to drive the development of TH2 cell responses[58]. Direct recognition of pathogens by CLRs expressed on lymphocytes, including γδ T cells[59],

NK cells[60] and B cells[61], can also induce the production of pro-inflammatory 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 cells[44].

Immunity to fungi. C-type lectins are well known for their ability to recognize 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 system[62]. 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 REFS[8,53]). Recently discovered components include JNK and CBLB (an E3 ubiquitin ligase that targets dectin 1, dectin 2, MCL and SYK[63–65]), both of which inhibit protective antifungal immune responses and are therefore 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 recognize fungal β-glucan and α-mannan[66]. Other newly identified components of C-type lectin-mediated signalling include the VAV proteins, which function as key proximal activators of the CARD9 pathway[67], and the ubiquitin ligase TRIM62, which is essential for CARD9 activity[68]. Polymorphisms in both of these molecules impact human disease[67,68]. Whereas phosphatases, including SHIP1 and SHP1, commonly downregulate C-type lectin-mediated responses[69,70] (see below), 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 recruitment[71].

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 infections[72], and are essential for the development of fungus-specific CD4+ T cell responses in the gastrointestinal tract[73]. 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 disease[76]. Soluble C-type lectins, such as

MBL, have also been implicated in intestinal homeostasis to commensal fungi[77]. 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 that impacts tissue-specific antifungal immunity[78]. 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 pathogens[79]. 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 immunity[80].

There is considerable interest in determining the involvement of individual C-type lectins in immunity to specific fungal pathogens, the ligands that are recognized and the effects that polymorphisms in the genes encoding these receptors have on human disease (reviewed elsewhere[55]). However, our understanding of these topics has yet to fully incorporate the genetic and non-genetic factors that influence antifungal immune responses in the host[81] or the interspecies fungal diversity that considerably impacts host responses and the relevance of specific C-type lectins[82]. Another complicating factor is the extensive interaction that occurs between C-type lectins and other PRRs following fungal recognition, which can increase or suppress specific responses[55]. For example, the recognition of *Fonsecaea* spp. by mincle suppresses the protective T cell responses that are induced by dectin 1 and dectin 2 during infection[83,84]. 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 surface[85].

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 recognize these microorganisms[86]. Several cell wall glycolipid ligands for C-type lectins have been defined — including trehalose dimycolate (TDM, which is recognized by mincle and MCL), phosphatidyl-inositol mannosides (which are recognized by DC immunoactivating receptor 1 (DCAR1; also known as CLEC4B1 in mice) and mannose-capped lipoarabinomannan (which is recognized by dectin 2 and DC-SIGN) — which primarily induce inflammatory and antimicrobial cellular responses through the SYK–CARD9 pathway in myeloid cells[86–88] (BOX 1). The stimulatory capacity of these ligands, and their ability to promote T cell immunity, have prompted interest in their use as immunological adjuvants (BOX 2). Indeed, the effectiveness of the widely used mycobacteria-based experimental adjuvant complete Freund's adjuvant involves mincle-mediated responses to TDM[89].

Despite their ability to induce robust responses to purified mycobacterial ligands and to respond to intact

Adjuvants

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

organisms in vitro, the role of individual CLRs in anti-mycobacterial immunity is less clear. Analyses 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 responses[86], 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 context[90]. The one exception is MCL, the phagocytic functions of which were shown to be essential for protective immunity to *Mycobacterium tuberculosis* in both mice and humans, although this was established in only one patient cohort[91]. Interestingly, deficiency of CARD9 renders mice extremely susceptible to mycobacterial infection[92], but similar susceptibility has not been observed in humans with functionally deficient mutants of this adaptor (A. 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 production in DCs, which has a key role in modulating infection-driven inflammatory pathology and mycobacterial control[93].

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*[94] and with *Klebsiella pneumoniae*[95], 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 pro-inflammatory cytokines[96]. 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, which influences homeostasis, and affect the development of inflammatory bowel disease. A genome-wide analysis revealed multiple host loci, including those encoding several C-type lectins, that affect the composition and function of the gut microbiome[98]. Several immunological 'circuits' have been described. For example, both dectin 1 and SIGNR3 (also known as CD209D) influence the function of regulatory T (T_{reg}) 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 growth[75], whereas SIGNR3 has an effect through direct interactions with the bacterial surface layer protein A[99]. DC-SIGN has been shown to recognize fucose-specific carbohydrates on the human gastric pathogen *Helicobacter pylori*, which suppresses inflammatory responses and drives the development of T_H2 cell-mediated immunity[100]. Contact between the epithelium and intestinal bacteria is controlled by the REG3 family of soluble bactericidal C-type lectins, which form pores in Gram-positive cell membranes[101].

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 the 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 ULBP1 (REF.[102]). 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 the modulation of host cytokine responses[103].

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 immune responses. 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 pathway, transfer of virus antigens to DCs and the induction of protective cytotoxic T lymphocyte (CTL) responses[104,105]. 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 virus[106] and herpes simplex virus[107].

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 cells[104,108]. 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 receptors[109]. 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 virus[108]. 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

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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 recognize 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.

as CLEC4G) — induces damaging pro-inflammatory responses that contribute substantially to the pathology of these infections[110–112]. CLEC5A has also been implicated in dengue virus-induced osteoclast activation and alterations in bone homeostasis[113]. Polymorphisms of DC-SIGN, and other C-type lectins, are associated with alterations in viral disease susceptibility and outcome in humans[114].

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 T_H2 cell polarization[115]. Several well-characterized C-type lectins have been implicated in these activities, including MBL, DC-SIGN and MMR, which can recognize 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 humans[116]. 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. The limited studies of parasite infections in knockout mice have largely failed to establish a clear role for the most well-characterized 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, was recently found to have an essential role in immunity by increasing macrophage activation and parasite killing during infection with *T. cruzi* and *Nippostrongylus brasiliensis*, respectively[117,118]. 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 Fc receptor γ-chain that impaired DC activation and the development of protective adaptive immunity[69].

Autoimmunity and inflammatory diseases

C-type lectins are increasingly being recognized 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 recognize 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 recognize DAMPs, thereby promoting inflammatory responses that can contribute to the pathology of these diseases (see the discussion of cell death, above). C-type lectins influence crucial aspects of B and T cell development; for example, the expression of CD69 is required for the development of functional T_{reg} cells[9], and LOX1 signalling in both DCs and B cells is required to induce B cell differentiation into class-switched plasmablasts[54]. 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.

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 threefold difference in gender susceptibility to rheumatoid arthritis, although the mechanisms behind this effect are unclear[119]. One of the most well-studied roles for soluble C-type lectins in arthritis is that of 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 cells[120]. Notably, under inflammatory conditions, aggrecan is degraded by ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) metalloproteinases and can become citrullinated; antibody and T cell reactivity to citrullinated aggrecan peptides is present in patients with rheumatoid arthritis and is thought to be causally related to pathology[121]. Polymorphisms influencing serum levels and activity of another soluble C-type lectin, MBL, have been suggested to be involved in the pathogenesis of arthritis, but this has not been supported by a recent meta-analysis or in murine models[122].

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 arthritis[123], and mice lacking this receptor show aberrant DC proliferation and differentiation that lead to the spontaneous development of autoimmune sialadenitis and enthesitis, as well as increased pathology during collagen-induced arthritis[124]. Moreover, the ability of DCIR to regulate the differentiation of IFNγ-producing T cells is required for the maintenance of bone homeostasis, as IFNγ was found to have chondrogenic and osteoblastogenic activity[125]. 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 unclear[126]. Although polymorphisms of MICL are not directly associated with rheumatoid arthritis, a subset of patients has MICL-specific autoantibodies, which are able to worsen disease when modelled in mice[126].

The pro-inflammatory 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, respectively[127,128]. In humans, the expression levels of both receptors positively correlate with disease
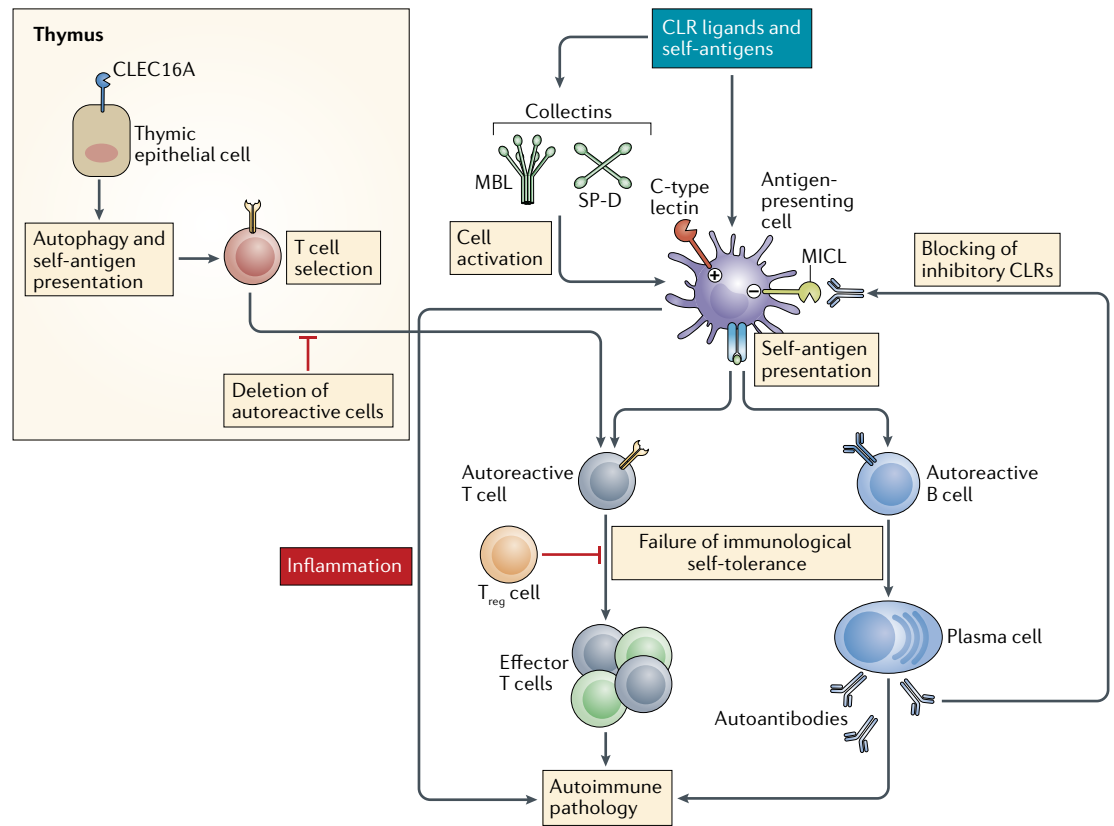
Fig. 4 | **C-type lectins in autoimmunity.** C-type lectins can both hasten and delay the progression of autoimmune disease. In a genetically predisposed individual, the recognition of C-type lectin receptor (CLR) ligands or self-antigens by soluble collectins (such as mannose-binding lectin (MBL) and surfactant protein D (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 myeloid inhibitory C-type lectin (MICL) regulate this activation pathway, and autoantibodies targeting these C-type lectins may worsen disease. C-type lectins are 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. T_{reg}, regulatory T.

severity[129,130]. Inhibition of NKG2D is similarly beneficial in murine models, presumably through its effect on IL-17 levels and through its cytotoxic effector functions (see above)[131]. Polymorphisms of NKG2D and its ligands have been associated with alterations in susceptibility to and severity of rheumatoid arthritis in humans[132].

Type 1 diabetes. CLEC16A is a membrane-associated endosomal protein, and the gene encoding it has been identified from genome-wide association studies (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 cells[133]. However, in a more recent study, the effects of CLEC16A were attributed to changes in the autophagy of thymic epithelial cells and its impact on thymocyte selection, which might explain the broad effects of variation in this C-type lectin in different types of autoimmunity[134]. Variants

of CLEC16A have also been associated with diseases including common variable immune deficiency disorder[135] and selective immunoglobulin A deficiency[136], 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-products[137,138]. Expression levels of LOX1 and MBL are key risk factors for the development of diabetic complications, including pulmonary fibrosis[139] 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 responses[140].

Genome-wide association studies
(GWAS). Genetic sequencing studies used to determine whether a genetic variant (normally a single-nucleotide polymorphism) found within a population is associated with a trait of interest, such as a specific disease.

Atherosclerosis. LOX1 is a receptor for modified lipoproteins, particularly oxidized low-density lipoprotein (oxLDL), that contributes substantially to the development of atherosclerosis and other cardiovascular diseases. LOX1 is upregulated on vascular endothelial cells under inflammatory conditions. This C-type lectin induces several cellular responses, including the production of reactive oxygen species and pro-inflammatory 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 thrombogenesis[141]. 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 of disease or protection from it[141,142]. Given the importance of LOX1 in cardiovascular disease, there is much interest in developing inhibitors of this receptor for therapeutic use[143] (BOX 2). Interestingly, statins, which are used clinically to reduce cholesterol biosynthesis, are also able to disrupt LOX1-mediated binding and internalization of oxLDL[144].

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 thrombosis[145]. 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 macrophages[147]. In humans, serum levels of and polymorphisms in SP-D correlate with the severity of cardiovascular disease[148]. In mouse models, DNGR1 has been implicated in promoting inflammation during the development of atherosclerosis by downregulating the production of IL-10 (REF.[149]). Mincle, which triggers inflammatory responses upon recognition of necrotic cells or cholesterol crystals[150], 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 pro-inflammatory mediators[151].

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 disorders[152]. Recent data, for example, have shown that the ability of dectin 1 to recognize fungi and trigger innate inflammatory and T_H17 cell responses contributes to the development of hypersensitivity pneumonitis[153]. Moreover, dectin 1 is involved in the induction of both eosinophilic and neutrophilic responses, as well as T_H2 cell and T_H17 cell differentiation, during fungal and house dust mite (HDM)-mediated allergic inflammation[154]. In fact, polymorphisms of dectin 1, MBL and SP-D are associated with susceptibility to severe asthma in humans[155,156]. Attention has focused on the unusual ability of dectin

2 to induce a SYK-dependent and PKCδ-dependent signalling pathway in response to HDMs, which results in the production of cysteinyl leukotrienes and other pro-inflammatory mediators, as well as IL-33, promoting allergic T_H2 and T_H17 cell responses[58]. 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 foods[157]. 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 T_H2 cell responses[158]. Mincle was shown to recognize cholesterol sulfate, which is present at high concentrations in epithelial barriers, leading to the induction of pro-inflammatory 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 understood[159].

Versican facilitates leukocyte recruitment during allergic responses by modifying the ECM, as described above[12]. 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 the pathology of the disease[12]. Leukocytes associated with allergy, including basophils and eosinophils, also express C-type lectins that influence their recognition of and response to allergens[160]. Notably, a predominant constituent of eosinophil secondary granules is the C-type lectin eosinophil major basic protein, 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 basophils[161].

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-22 (REF.[162]), a key cytokine that has been linked to the 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 priming[163]. Similarly, in the development of SLE, CD72 inhibits B cell responses upon recognition of self-antigen in the form of Sm ribonucleoproteins, which limits the production of pathogenic auto-antibodies[164]. By contrast, in murine models of autoimmune uveitis, mincle and dectin 1 were shown to drive pro-inflammatory T_H17 cell responses that promote development of the disease, although it is unclear what

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ligands are being recognized by these receptors in these autoimmune disease models[165,166].

Concluding remarks

C-type lectins are an extraordinary superfamily of proteins that recognize 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 those underlying 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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