REVIEW

Myeloid C-type lectin receptors in skin/mucoepithelial diseases and tumors

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Abstract
Myeloid C-type lectin receptors (CLRs), which consist of an extracellular carbohydrate recognition domain and intracellular signal transducing motif such as the immunoreceptor tyrosine-based activation motif (ITAM) or immunoreceptor tyrosine-based inhibitory motif (ITIM), are innate immune receptors primarily expressed on myeloid lineage cells such as dendritic cells (DCs) and Mφs. CLRs play important roles in host defense against infection by fungi and bacteria by recognizing specific carbohydrate components of these pathogens. However, these immune receptors also make important contributions to immune homeostasis of mucosa and skin in mammals by recognizing components of microbiota, as well as by recognizing self-components such as alarmins from dead cells and noncanonical non-carbohydrate ligands. CLR deficiency not only induces hypersensitivity to infection, but also causes dysregulation of mucocutaneous immune homeostasis, resulting in the development of allergy, inflammation, autoimmune, and tumors. In this review, we introduce recent discoveries regarding the roles of myeloid CLRs in the immune system exposed to the environment, and discuss the roles of these lectin receptors in the development of colitis, asthma, psoriasis, atopic dermatitis, and cancer. Although some CLRs are suggested to be involved in the development of these diseases, the function of CLRs and their ligands still largely remain to be elucidated.

KEYWORDS
C-type lectin receptor, colitis, asthma, psoriasis, atopic dermatitis, cancer, fungal infection, mycobacterium infection, mucosal immunity, innate immunity

1 INTRODUCTION

C-type lectins (CTLs) are one of pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) of pathogens. CTL molecules contain a carbohydrate recognition domain (CRD) in the C-terminus that recognizes specific carbohydrate structures on pathogens in a Ca²⁺-dependent manner. Many CTLs also contain signaling motifs, such as immunoreceptor tyrosine-based activation motif (ITAM) or immunoreceptor tyrosine-based inhibitory motif (ITIM) in the cytoplasmic portion, or recruit an adaptor protein that contains ITAM, thus acting as a signaling receptor for pathogens (CTL receptor, CLR; Table 1). Some family members can recognize molecules other than carbohydrates in a Ca²⁺-independent manner. CTLs are consisted of more than 100 family molecules and divided into 16 groups.³ Myeloid CLRs belong mainly to groups 2, 5, and 6 of the CTL family. Among them, the genes encoding DCAR2, DCIR, DCAR1, DECTIN-2, CLEC12B, CLEC2, DNGR-1, CLEC1A, DECTIN-2, and LOX-1 map to the Dectin-1 and Dectin-2 loci.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AD, atopic dermatitis; AHR, airway hypersensitivity; cDC, conventional DC; CRD, carbohydrate recognition domain; CTL, C-type lectin; CLR, CTL receptor; DC, dendritic cell; DSS, dextran sulfate sodium; HDM, house dust mite; IBD, inflammatory bowel diseases; ILC3, type 3 innate lymphoid cell; IMQ, imiquimod; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; MDSC, myeloid-derived suppressor cell; PRR, pattern recognition receptor; ROS, reactive oxygen species; TDM, trehalose 6,6′-dimycolate.

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| Name               | Other names                          | Gene symbol (Chr. #)               | Signaling motif | Ligand                                      | Expression                      | Function                                                                 |
|--------------------|-------------------------------------|-----------------------------------|-----------------|---------------------------------------------|----------------------------------|---------------------------------------------------------------------------|
| CLEC1A             | C-type lectin-like receptor-1, CLEC1, MelLec | Clec1a (Chr. 6, Dectin-1 cluster) | No known motif  | DHN-melanin                                 | Endothelial cells, DC          | Immune response against *Aspergillus fumigatus*; Allograft tolerance       |
| CLEC1B             | C-type lectin-like receptor-2, CLEC1B | Clec1b (Chr. 6, Dectin-1 cluster) | Hemi-ITAM       | Podoplanin, rhodocytin                       | Platelets, megakaryocytes, Kupfer cells | Lymphvasculogenesis; maintenance of hematopoetic stem cells; regulate tumor cell growth |
| CLEC12B            | C-type lectin-like receptor-12B      | Clec12b (Chr. 6, Dectin-1 cluster) | ITIM            | Minor binding to terminal GlcNAc, GalNAc and galactose | In vitro differentiated Mφ, Caveolin-1-dependent expression | Inhibition of the NK receptor NKG2D-mediated signaling                     |
| DCAR1              | Mouse dendritic cell immune activating receptor 1, Apra1 | Clec4b2 (Chr. 6, Dectin-2 cluster) | None            | No known ligand                             | CD8+ DC, CD11b+ myeloid cells | Enhancement of inflammatory response                                      |
| DCAR2              | Dendritic cell immunoactivating receptor, DCAR, Dcar2, Api2, DCARbeta | Clec4b1 (Chr. 6, Dectin-2 cluster) | None, Association with ITAM-containing FcRg | Phosphatidylinositol mannosides (PIM) | Mφ, Mo-derived cells | T cell response against mycobacteria                                      |
| DCIR               | Dendritic cell immune-receptor, DCIR1 | Clec4a2 (Chr. 6, Dectin-2 cluster) | ITIM            | Sulfated lactose, LacNAc, biantennary N-glycans | DC, Mφ, Neu, B cells | DC and osteoclast differentiation; immunity to tuberculosis; attachment of HIV and HCV to facilitate infection |
| DEC-205            | CD205                               | Ly75 (Chr. 2)                     | Tyr-based motif | Keratins                                    | Mature DC, LC, thymic epithelial cells | Endocytosis of Ags; Ag cross presentation; recognition of dead cells     |
| DECTIN-1           | Dendritic cell-associated C-type lectin-1, CLECSF12 | Clec7a (Chr. 6, Dectin-1 cluster) | Hemi-ITAM (YxxL motif) | α-glucans, galectin-9, tumor-specific carbohydrate | DC, Mφ, LC | Defense against fungi and mycobacteria; tumor promotion; protection against tumors |
| DECTIN-2           | Dendritic cell-associated C-type lectin-2, CLEC6A | Clec4n (Chr. 6, Dectin-2 cluster) | None, association with ITAM-containing FcRg | α-mannans, Man-LAM | DC, Mφ, LC | Defense against fungi and mycobacteria; house dust mite-induced allergy |
| DNGR-1             | Dendritic cell natural killer lectin group receptor-1 | Clec9a (Chr. 6, Dectin-1 cluster) | Hemi-ITAM       | Necrotic cells, mycobacteria                | DC, Mo                          | Necrotic cell Ag cross presentation; defense against *Mycobacterium*       |
| LANGERIN           | CD207                               | Cd207 (Chr. 6)                     | Proline-rich motif | Mannose, fucose, β-glucan               | LC                             | Formation of Birbeck granules; Agcross-presentation; antifungal defense  |
| LOX-1              | Lectin-like oxidized low-density lipoprotein receptor-1, CLEC8A, OLR1, HLOX-1 | Clec8a (Chr. 6, Dectin-1 cluster) | No known motif | Oxidized low-density lipoprotein            | Endothelial cells, Mo, platelets, cardiomyocytes | Progression of atherosclerosis; tumorigenesis                     |

(Continues)
| Name | Other names | Gene symbol(Chr. #) | Signaling motif | Ligand | Expression | Function |
|------|-------------|---------------------|----------------|--------|------------|----------|
| MCL  | Mφ C-type lectin, CLEC8F8, DECTIN-3 | Clec4d (Chr. 6, Dectin-2 cluster) | None, association with ITAM-containing FcRγ | TDM, Glucurono-xylomannan | Neu, Mo, Mφ | Defense against Mycobacterium and Cryptococcus |
| MDL-1 | Myeloid DAP12-associating lectin-1 | Clec5a (Chr. 6) | None, association with ITAM-containing DAP12 | Dengue virus particle | Mo, Mφ, osteoclast, Neu | Dengue virus receptor; involvement in inflammation, osteoclastogenesis, arthritis and atherosclerosis; promotion of Mφ survival |
| MGL1 | Mφ galactose-type C-type lectin-1, Mφ asialoglycoprotein-binding protein 1, MGL, CD301a | Clec10a (Chr. 11) | Hemi-ITAM (YxxL motif) | Terminal Gal and GalNAc, MUC1, Siglec-1 | Immature DC, Mφ | Regulation of effector T cell signaling; Ag presentation; suppression of Treg; tumor progression; enhancement of TNF and IL-10 production |
| MICL | Myeloid inhibitory C-type lectin-like receptor, CLL-1, DCAL-2, CD371 | Clec12a (Chr. 6, Dectin-1 cluster) | ITIM | Uric acid crystals | DC, Neu, eosinophils, Mo | Recognition of apoptotic cells; leukemia cancer stem cell marker; Ag uptake and cross-presentation |
| MINCLE | Mφ inducible C-type lectin, CLEC8F9 | Clec4e (Chr. 6, Dectin-2 cluster) | None, association with ITAM-containing FcRγ | TDM, SAP130 | Mφ, DC, Neu, B cells | Defense against fungi and mycobacteria; recognition of damaged cells |
| MR   | Mannose receptor, mannose receptor C-type 1, MRC1, Mφ mannose receptor, MMR, CD206 | Mrcl (Chr. 2) | No known motif | Man, Fuc, GalNAc, lysosomal enzymes, IPA, Gal-3-So4, GalNAc-4-So4, lutropin, CD45, sialoadhesin, MUCIII, M. tuberculosis ManLAM | DC, LC, Mφ, Mo, endothelial cells | Activation of Th2 differentiation and suppression of Th1 differentiation; induction of cytokines in collaboration with TLR2 or DECTIN-1 |
| SIGN-R3 | Mouse homologue Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), CD209, CD209d, (DC-SIGN in humans) | Cd209d (Chr. 8) (DC-SIGN: Chr. 19 in humans) | Hemi-ITAM (YSDI motif) | Terminal Man and Fuc, Lewisα, ManLAM, Lipomannan,LDNF, HIV-1 gp120, ICAM-2, -3 | DC, Mφ | Pathogen recognition; Ag uptake; DC migration; T cell interaction |

DC, dendritic cells; LC, Langerhans cells; Mo, monocytes; Mφ, macrophages; Neu, neutrophils
cluster loci on mouse chromosome 6 (Table 1) and chromosome 12 in humans. Genes encoding other myeloid CLRs, such as DC-SIGN (human Chr. 19) and its mouse homologue SIGNR3 (mouse Chr. 8), LANGERIN, MGL, MDL-1, DCAL-1, MR, and Dec-205 map to other chromosomes. These molecules are expressed as membrane proteins in myeloid cells including monocytes, Mψs, and dendritic cells (DCs) (Table 1).

Many CLRs encoded in the Dectin-1 and Dectin-2 cluster loci contain ITAM or ITIM in the cytoplasmic domain, suggesting that they transduce signals that regulate cellular function. Some molecules, such as DCAR2, Dectin-2, MCL, and MINCLE, have no ITAM but form a complex with ITAM-containing FcRy or DAP10/12 to transduce signals. Upon activation of ITAM-containing CLRs, the SYK kinase is recruited to ITAM and activates CARD9-BCL10-MALT1 complex, leading to downstream activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation. NY-κB activation induces various inflammatory cytokines and chemokines, including IL-1β and IL-23, which promote Th17 cell differentiation and IL-17A and IL-17F production from γδ T cells and type 3 innate lymphoid cells (ILC3s). On the other hand, ITAM-containing CLRs, including DCIR, recruit a tyrosine phosphatase such as SHP-1 or SHP-2 to ITIM and inhibit tyrosine phosphorylation, thereby blocking signals induced by PRRs and cytokines.4–6 However, DCIR also transduces a positive signal to sustain type 1-IFNα-induced STAT1 activation in DCs.7 By contrast, CLEC1A and LOX-1 contain no known signaling motifs.

Many ITAM-containing CLRs encoded in the Dectin-1 and Dectin-2 cluster loci are thought to play important roles in the host defense against pathogens (Table 1, and see reviews 2 and 3). Upon fungal infection, Dectin-1 recognizes β-(1, 3)-glucans on the cell wall and activates SYK through ITAM phosphorylation.8 Dectin-2 recognizes α-mannans, another PAMP of fungi, and also activates SYK by recruiting FcRγ.9 Bacterial components, such as trehalose 6,6′-dimycylolate (TDM) in mycobacteria, can activate MCL.10 SYK activation induces reactive oxygen species (ROS) production, contributing to the eradication of fungi and bacteria. Furthermore, SYK-induced cytokines, such as IL-23 and IL-1β, induce differentiation and production of IL-17A and IL-17F from Th17 cells, γδ T cells, and ILC3s. Th17 cytokines play important roles in the eradication of fungi and bacteria by recruiting neutrophils and inducing production of antimicrobial proteins.11–14

Myeloid CLRs have attracted researchers’ attention because recent studies have suggested that they play crucial roles in maintaining immune homeostasis and controlling tumor development, as well as protecting against infection. Because myeloid CLRs can recognize both pathogens and commensal bacteria and fungi, they are important for maintaining the commensal microflora of the skin and the mucosal epithelial surface of the intestine and lungs. Dysregulation of these microbiota can cause diseases. Furthermore, some myeloid CLRs recognize endogenous molecules to regulate cell differentiation,4,15 and have been suggested to play important roles in the development of inflammatory diseases and tumors by recognizing molecules released by dead cells16,17 or expressed on tumor cells.18 Hence, in this review, we will discuss the roles of myeloid CLRs in the development of diseases of the skin and mucosal epithelial tissues as well as in the development of tumors.

2 MYELOID CLRS IN INTESTINAL MUCOSAL IMMUNITY

2.1 Colitis

To maintain mucosal homeostasis, the intestinal immune system has to deal with contradictory requirements; the system must be tolerant of commensal microbiota and food components, but fight against invading pathogens. Innate immune receptors such as CLRs and TLRs sense PAMPs not only on pathogens but also on commensal microbiota, and induce ROS, antimicrobial proteins, cytokines, and chemokines that play important roles in the eradication of these pathogens. At the same time, excess cytokines and chemokines cause inflammatory bowel diseases (IBD), including Crohn’s disease and ulcerative colitis. Thus, a fine balance between inflammatory (anti-pathogen) and anti-inflammatory (tolerogenic) immunity is required for homeostasis of intestinal immunity. However, the mechanisms regulating this balance remain largely obscure.

DECTIN-1 (gene symbol: Clec7a) is the receptor for β-glucans, which are main components of the fungal cell wall and abundant in the daily diet. Interestingly, unlike other CLRs such as Dectin-2 and DcR1, Dectin-1 is highly expressed in Mψs and monocytes of the intestinal lamina propria. Accordigly, this molecule is thought to serve some functions related to intestinal mucosal immunity. Indeed, loss of Dectin-1 impairs Candida albicans-specific CD4+ T cell development in gastrointestinal-associated lymphoid tissues,19 although Dectin-1 is not crucial for defense against intestinal Candida albicans infection.20 Some pathogenic fungi, such as Candida tropicalis, expand in Clec7a−/− mouse intestine and exacerbate the development of dextran sulfate sodium (DSS)–induced colitis.21 In the absence of fungal colonization, however, Clec7a−/− mice develop much milder intestinal inflammation than wild-type mice after DSS administration.22 This is because the regulatory T cell population is expanded in Clec7a−/− colon due to proliferation of a Treg-inducing commensal bacterium, Lactobacillus murinus. Lactobacillus murinus proliferates in Clec7a−/− mice, because levels of the antimicrobial protein calprotectin S100A8, which is induced downstream of DECTIN-1 signaling through induction of IL-17F and can inhibit Lactobacillus growth, is reduced in these mutant mice.22,23 Therefore, Dectin-1 acts as a double-edged sword in the regulation of colitis development; it is necessary for protection against fungal infection, but excess Dectin-1 signaling suppresses Treg cell differentiation and induces inflammation. Thus, fungal infection may cause inflammation not only via direct pathogenic effects but also by reducing the abundance of Treg cells in the intestine. Administration of short chain β-glucans such as laminarin, a component of the brown alge kombu that antagonizes binding of fungal long chain β-glucans to DECTIN-1, can ameliorate DSS–induced colitis by increasing the population of Treg cells (20).

In addition, DECTIN-1 can form a receptor complex with GALECTIN-3 and Fcγ-RIIB to recognize the mucin MUC2, enhancing oral tolerance by inhibiting NF-κB activation and inflammatory cytokine production in intestinal DCs.24 GALECTIN-3 promotes the assembly by recognizing N-glycan structures of not only DECTIN-1, but also Dectin-2 and SIGN-R1.25
Deficiency of CARD9, a downstream adaptor protein of ITAM-mediated CLR signaling, also causes intestinal fungal expansion and aggravates colitis; oral inoculation of *Lactobacillus murinus* can ameliorate this intestinal inflammation. The authors of that study suggested that reduced levels of IL-22, which is important for the recovery from colitis, is responsible for the increased susceptibility to colitis rather than increased fungal growth in *Card9*−/− mice, and showed that IL-22 is induced by aryl hydrocarbon receptor ligands produced by commensal bacteria including *Lactobacillus* family members.

DECTIN-1 is expressed in freshly isolated human intestinal epithelial cells (IECs) and human IEC lines, but not in the analogous mouse cells. Stimulation of human IECs with β-glucans induces IL-8 and CCL2 secretion, which can be blocked by SYK inhibition, suggesting involvement of IECs in the development of colitis in humans. CLEC7A expression is up-regulated in inflamed colons of IBD patients, and 2 single-nucleotide polymorphisms in CLEC7A are correlated with medically refractory ulcerative colitis. Thus, DECTIN-1 plays important roles not only in host defense against infection, but also in maintaining intestinal homeostasis under physiological conditions. However, additional studies are still needed to fully understand the roles of this molecule completely in the homeostasis of human intestinal immunity.

Other myeloid CLRs are also implicated in the development of colitis. MGL1, expressed in colonic lamina propria F4/80-high cells, binds *Streptococcus* species and *Lactobacillus* species to induce IL-10 production in vitro. Mice lacking this molecule develop more severe inflammation after DSS-treatment, accompanied with impaired IL-10 secretion. Although MCL and DCIR also bind some intestinal commensal microbiota, mice deficient in these molecules develop slightly more severe DSS-induced colitis. Another report showed...
that DCIR-deficient mice develop even milder colitis, with reduced neutrophil-attracting chemokine MIP-2 and decreased accumulation of neutrophils.\textsuperscript{31} MR-expressing mouse intestinal M\textsubscript{0}Ns contribute to wound healing in DSS-induced colitis.\textsuperscript{32} SIGN-R1, the mouse homolog of human DC-SIGN, synergizes with TLR4 to respond to LPS, and deficiency of SIGN-R1 impairs commensal bacteria-induced pro-inflammatory cytokine production and attenuates intestinal inflammation after DSS administration.\textsuperscript{33} Another DC-SIGN homolog, SIGN-R3, also recognizes glycan structures on commensal fungi and \textit{Mycobacterium tuberculosis}. Mice deficient in this molecule are more sensitive to \textit{M. tuberculosis} infection and develop more severe colitis with an enhanced TNF production.\textsuperscript{34} The detailed functional roles of these myeloid CLRs remain to be elucidated.

### 3 | MYELOID CLRS IN PULMONARY MUCOSAL IMMUNITY

#### 3.1 | Asthma and allergic diseases

Asthma, one of most common chronic respiratory diseases, is associated with airway inflammation and remodeling. Possible alterations of asthmatic patient airway structure include mucous gland and goblet cell hyperplasia, modification of epithelial cells, subepithelial fibrosis, constriction of airway smooth muscle, and changes in blood vessels.\textsuperscript{35} Numerous cytokines, including IL-9, IL-13, IL-17, IL-22, IL-25, and other inflammatory mediators, are involved in the airway remodeling.\textsuperscript{36,37} Despite being classified as a single disease, the term "asthma" subsumes pathologically distinct complex diseases, often accompanied by other morbidities, complicating patient state and decisions about treatment regimen.\textsuperscript{38} Frequently, asthma originating in childhood may continue at older ages. To a large extent, asthma developed in children is associated with allergy and atopic disease. Atopic asthma is caused by type 2 immune responses with enhanced IgE production, followed by eosinophilia and mast cell activation.\textsuperscript{39} Asthma can also be diagnosed at any age in adulthood. However, the majority of adult-diagnosed asthma is Th2-low and non-atopic, and is often associated with high neutrophil concentrations and elevated Th17-related responses.\textsuperscript{40,41} Importantly, Th2-high and Th2-low forms of asthma exhibit distinct responses to corticosteroid treatment; Th2-high asthmatics respond to this treatment, whereas Th2-low patients are refractory.\textsuperscript{38} CLRs are thought to be involved in both forms of asthma (Fig. 2).

##### 3.1.1 | \textit{Aspergillus fumigatus}-associated asthma

Sensitization to allergens from \textit{Aspergillus fumigatus} is often associated with asthma. A study by Bozza et al. revealed that various fungal components are responsible for different Th-type responses and cytokine production.\textsuperscript{42} Secreted proteins such as metalloprotease (Mep1p), superoxide dismutase (Sod1p), and ribonuclease (RNUp) from the fungus induce Ag-specific Th2-cell differentiation. IL-5 and IL-13 from Th2 cells promote IgE production from B cells, which leads to activation of mast cells and basophils by the immune complex to produce various inflammatory mediators such as leukotrienes and prostaglandins. Th2 cells also recruit eosinophils and mast cells and promote production of these inflammatory mediators. Furthermore, fungal and house dust mite (HDM) proteases and a fungal glycosphingolipid release IL-33 from epithelial cells and M\textsubscript{0}Ns, respectively.\textsuperscript{43,44} IL-33 directly induces the production of inflammatory mediators from basophils, mast cells, and eosinophils, and also indirectly induces inflammatory signaling by promoting Th2 cytokine production from Th2 cells, ILC2, mast cells, and basophils, mostly resulting in development of steroid-sensitive asthma.\textsuperscript{42,45–47} Although some reports have suggested that this phenomenon is involved in steroid resistant asthma\textsuperscript{48} (Fig. 2).

Both DECTIN-1 and DECTN-2 are predominantly involved in the antifungal response, and their expression levels increase upon infection with the hyphal form of \textit{Aspergillus fumigatus}.\textsuperscript{8,9,49,50} Interestingly, polysaccharides from the fungal cell wall, namely, \(\beta\)-1,3-glucans and \(\alpha\)-mannans, can induce Th17 cell differentiation by inducing cytokines, including IL-1\(\beta\) in DCs through activation of DECTIN-1 and IL-23 in M\textsubscript{0}Ns through activation of DECTIN-2.\textsuperscript{51,52} Th17 cell-derived IL-17A and IL-17F recruit neutrophils to eradicate fungi, and at the same time, induce steroid-resistant lung inflammation.\textsuperscript{53} Upon infection with \textit{Aspergillus fumigatus}, neutrophils are activated in an autocrine manner by expressing IL-17A and IL-17RC via DECTIN-2-mediated induction of IL-6 and IL-23.\textsuperscript{49,54} DECTIN-2 is also involved in Th2-type asthma in response to both \textit{Aspergillus fumigatus} and HDM.\textsuperscript{55,56} Barrett et al. revealed that DECTIN-2 can stimulate production of cysteiny1 leukotrienes by DCs in response to \textit{Aspergillus fumigatus} extract.\textsuperscript{56} These leukotrienes produced by DCs are potent mediators of pulmonary inflammation in bronchial asthma and can augment Th2 sensitization.\textsuperscript{55,56} DECTIN-1 is also a potent inducer of leukotrienes in mast cells and M\textsubscript{0}Ns after stimulation with zymosan.\textsuperscript{26,27} Furthermore, DECTIN-1 induces IL-22, which aggravates airway hypersensitivity (AHR) by promoting the production of proallergic chemokines and mucus, along with IL-17A and IL-17F.\textsuperscript{57} \(\beta\)-Glucans from \textit{Aspergillus versicolor}, a close relative of \textit{Aspergillus fumigatus}, worsens HDM-induced AHR by causing a mixed inflammatory reaction involving both Th2 and Th17 cells, accompanied by increased number of neutrophils and eosinophils.\textsuperscript{58} Similar enhancement of asthma is observed when mice are treated with a combination of \(\beta\)-glucans and LPS.\textsuperscript{59} Although acute exposure of \textit{Clec7a}{\textsuperscript{\textdagger}} mice to \textit{Aspergillus fumigatus} increases fungal invasion of the fungus, it induces milder allergic response with reduced neutrophil infiltration.\textsuperscript{57} Thus, DECTIN-1 (and possibly DECTN-2) are primarily involved in the induction of Th17 responses in asthma accompanied by high neutrophilic infiltration, although direct evidence for the involvement of DECTIN-2 in asthmatic Th17 responses is lacking. On the other hand, the asthmatic response of allergic bronchopulmonary aspergillosis (ABPA) patients to \textit{Aspergillus fumigatus} mainly is mediated not by DECTIN-1-induced neutrophilia but by allergic Th2-type responses induced by fungal proteases.\textsuperscript{60} In addition, \textit{Aspergillus fumigatus}-derived proteases and neutrophil elastase can cleave DECTIN-1, DECTIN-2, and MINCLE, suppressing antifungal immune responses and promoting development of ABPA in cystic fibrosis patients.\textsuperscript{61}

Among other CLRs, DC-SIGN, the receptor for galactomannans, is also suggested to take part in \textit{Aspergillus fumigatus}-induced immune response.\textsuperscript{62}
Anti-fungi

**FIGURE 2** The roles of CLRs in asthma. Ags from *Aspergillus fumigatus* and HDM activate DCs to induce differentiation of Th2 cells, resulting in the development of Th2-high asthma through activation of mast cells, eosinophils, NH cells, ILC2s, and basophils. On the other hand, PAMPs from these microbes activate CLRs such as DECTIN-1 and DECTIN-2, leading to the differentiation of Th17 cells and activation of \( \gamma \delta \) T cells and ILC3s. IL-17A and IL-17F produced in these cells induce inflammation in the lungs by recruiting neutrophils, that is a characteristic of Th2-low, steroid resistant asthma. IL-22 produced in these cells, as well as IL-17A and IL-17F, is involved in mucus production and epithelial proliferation. DECTIN-1, DECTIN-2, MR, and DC-SIGN also take part in the activation of Th2 cells, facilitating the development of Th2-high, steroid-sensitive asthma responses by recognizing galactomannans on *Aspergillus fumigatus*.\(^{54,62}\) However, its role in allergy-related processes remains to be elucidated.

3.1.2 HDM-associated asthma

HDMs are another widespread cause of AHR response and allergy.\(^{63}\) HDM allergens include proteases of *Dermatophagoides pteronyssinus* (Der p 1, Der p 3, Der p 6, and Der p 9) and of *Dermatophagoides farina* (Der f 1 and so on), which can induce production of inflammatory cytokines, breakage of epithelial barriers, and stimulation of airway smooth muscle proliferation in asthmatic patients.\(^{63}\) Some components of HDMs, such as chitin and \( \beta \)-glucans, are thought to act as PAMPs, resulting in activation of immune responses via several pathways including CLRs.\(^{64}\) DECTIN-1 on CD11b\(^+\) DCs binds to components of HDM extracts and modulates both Th2- and Th17-related immune responses; the production of IL-5, IL-13, and IL-17A, as well as chemokines CCR7, CCL3, and CCL4, is reduced in Clec7a\(^{-/-}\) mice upon HDM exposure.\(^{65}\) although the ligands for DECTIN-1
remain to be identified. Data concerning the role of chitin in allergic responses are very limited. Da Silva et al. showed that mammalian chitinase cuts originally intact molecules into pieces. Depending on their sizes, these pieces are recognized by DECTIN-1 in collaboration with TLR2, resulting in production of TNF, or by DECTIN-1 and MR, resulting in production of IL-10. FIBCD1 has been reported as a receptor for chitin, but its role in asthma remains to be elucidated.

Components of HDM extract also trigger cytotoxic leukotriene generation by CD11c+ DCs through the activation of the DECTIN-2–SYK pathway, and activates Th2 immune responses. Moreover, DECTIN-2–blocking Abs ameliorate Th2 inflammation through the attenuation of inflammatory cytokines such as IL-4, IL-5, and IL-13, and chemokines CCL22 and CCL17. DC-SIGN also promotes Th2 polarization after stimulation with Der p 1 by up-regulating indoleamine 2,3-dioxigenase activity. These pieces are recognized by DECTIN-1 in collaboration with TLR2, resulting in production of TNF, or by DECTIN-1 and MR, resulting in production of IL-10. FIBCD1 has been reported as a receptor for chitin, but its role in asthma remains to be elucidated.

The role of MR and DC-SIGN in the HDM-related response was previously reviewed by Hadebe et al. CD206 and DC-SIGN are receptors for HDM allergens (Der p 1 and Der p 2). CD206 induces Th2 polarization after stimulation with Der p 1 by up-regulating indoleamine 2,3-dioxigenase activity. DC-SIGN also promotes Th2 cell polarization upon interaction with Der p 1, because the protease cleaves DC-SIGN, which is in turn important for Th1 differentiation.

These observations suggest that CLRs play versatile roles in the development of asthma. CLRs such as DECTIN-1 and DECTIN-2 are primarily important for the defense against allergic fungal infection, but they also promote asthma pathogenesis by promoting Ag-specific allergic responses. In particular, these CLRs make important contributions to the development of Th2-low, steroid-resistant asthma by promoting Th17 immune responses. Thus, suppression of CLRs should be beneficial for the treatment of asthma, but caution is necessary because this strategy may also promote fungal growth.

### 4 | MYELOID CLRS IN CUTANEOUS IMMUNITY

#### 4.1 | Psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by thickening and redness of the skin associated with keratinocyte hyperproliferation, skin inflammation with inflammatory cell infiltration in the epidermis and dermis, and (in severe cases) aseptic abscess formation. Cytokines such as IL-23, IL-17A, and TNF play important roles for the pathogenesis of the disease, and the Abs against these cytokines are effective in treating the disease. Innate immune responses play important roles in mouse models. Imiquimod (IMQ), a TLR7 ligand, induces psoriasiform dermatitis in mice by inducing IL-23 from Langerin-negative conventional DCs (cDCs), followed by downstream induction of IL-17A. IL-17A is mainly produced by γδ T cells and ILC3, but not by αβ T cells. IL-17F is also involved in the development of dermatitis. Interestingly, IL-36α may be important for the induction of IL-23. IMQ directly induces IL-36α in bone marrow-derived Langerhans cells and GM-CSF-induced DCs, and IL-36α acts on bone marrow-derived Langerhans cells and keratinocytes to produce IL-23, IL-1β, and chemokines such as CCL20, CXCL1, and CXCL2, which recruit γδ T cells and ILC3 and induce IL-17A in these cells. Thus, IL-23 is induced directly in cDCs by IMQ, and indirectly in LCs and keratinocytes through induction of IL-36α. Because IL-36α is induced not only by IMQ but also by β-glucans from *Candida albicans*, fungal infection may also be involved in the development of dermatitis. It is likely that various innate immune receptors such as TLRs and CLRs expressed on the cell surface of LCs and DCs of the skin recognize PAMPs of bacteria and fungi, as well as alarmins derived from dying cells, and induce cytokines and chemokines including IL-36α, IL-23, IL-1β, and CCL20. Thus, CCL20 recruits γδ T cells and ILC3 to inflammatory sites, and IL-23 and IL-1β activate these cells to produce IL-17A, IL-17F, and IL-22. This leads to recruitment of neutrophils and production of various inflammatory cytokines and chemokines including TNF, G-CSF, IL-1α, CXCL1, and CXCL2 from keratinocytes and fibroblasts, causing inflammation and promoting keratinocyte proliferation, ultimately resulting in hyperplasia of the skin (Fig. 3). The antimicrobial protein LL37, which is produced by keratinocytes, is thought to activate TLR7 and TLR8 by forming a complex with RNA. Thus, innate immune responses, but not acquired immune responses, may play central roles in the development of psoriasis. After initiation of inflammation, however, various inflammatory cytokines may also activate immune cells of the acquired immune system, enhancing the inflammatory processes by forming an amplification loop.

Involvement of CLRs is also suggested in the development of psoriasiform dermatitis and arthritis in SKG mice. Administration of β-glucans or mannans evokes these symptoms in these mice, which do not develop any symptoms under SPF conditions, and the development of arthritis is suppressed in Clec7a−/− mice, suggesting that innate immunity triggers the development of Ag-dependent autoimmunity. Innate immune signaling has been suggested to activate complement pathways and produce C5a, which stimulates Mφs to produce IL-6 and GM-CSF, which in turn promote Th17 differentiation. Induction of IL-17A in Th17 cells is strictly TCR dependent, in contrast to the situation in γδ T cells or ILC3s. Treatment of psoriatic patients with corticosteroids or biologics targeting activated T cells or costimulation of T cells is clinically effective, suggesting that Th17 cells other than γδ T cells and ILC3s may also be involved in the development of psoriasis. A Mφ mannose receptor (MR) is expressed on immature DCs, but not on mature DCs or Langerhans cells. MR+ inflammatory dendritic epidermal cells are present in samples of skin from patients with atopic dermatitis (AD) or psoriasis, and use this receptor for receptor-mediated endocytosis of mannans. MR is suggested to regulate the development of psoriasiform dermatitis in mannan–injected mice, because MR-deficient mice develop more severe mannan–induced dermatitis, associated with the reduced production of ROS, which is important for the differentiation of immunosuppressive M2 Mφs. On the other hand, MR is expressed in CD163+ dermal Mφs together with...
FIGURE 3  The roles of CLRs in psoriasis. PAMPs from pathogens or commensal microbiota or alarmins from dead skin cells activate CLRs and TLRs such as DECTIN-1 or TLR7 on Langerhans cells (LCs), leading to production of proinflammatory cytokines including IL-36α, IL-23, and IL-1β. IL-36α also induces IL-23, IL-1β, and CCL20 in LCs and keratinocytes. Then, CCL20 recruits γδ T cells and ILC3 to the inflammatory sites, and IL-23 and IL-1β activate these cells to produce IL-17A, IL-17F, and IL-22. These cytokines recruit neutrophils and activate keratinocytes to produce various inflammatory cytokines, chemokines, and antimicrobial peptides such as TNF, G-CSF, CXCR2, LL37, and REG3A, causing development of inflammation and keratinocyte proliferation. These chemokines and cytokines further activate not only γδ T cells and ILC3 but also αβ T cells to enhance these inflammatory processes, forming an amplification loop.

4.2  Atopic dermatitis

AD is a chronic inflammatory skin disease associated with intense itch and recurrent eczematous lesions. The pathophysiology of AD is complex and multifactorial, and barrier dysfunctions of the skin such as caused by mutations in FILAGGRIN and enhanced cell- and IgE-mediated immune responses caused by sustained infection of bacteria and fungi are thought to be critically involved in the pathogenesis.80,91

AD patients have an elevated susceptibility to infection with bacteria, fungi, and viruses,90,91 and CLRs play important roles in the...
protection of pathogen invasion and pathogenesis of dermatitis. Among these pathogens, the best characterized is *Staphylococcus aureus*, which is detected in approximately 90% patients and is associated with disease exacerbation. The non-myeloid CTL mannose-binding lectin contributes to defense against this bacterium by activating the complement lectin pathway via an interaction with specific polysaccharide structures. *Malassezia*, a commensal fungus on the skin, is also thought to cause AD by producing a variety of immunogenetic proteins that elicit specific IgE immune responses.92,93 MINCLE, expressed on activated phagocytes, can recognize α-mannosyl residues on *Malassezia*, resulting in the activation of Mfs to produce inflammatory cytokines and chemokines.94 Mast cells from AD patients also express MINCLE, and upon exposure to *Malassezia*, MINCLE expression, and IL-6 secretion are enhanced.95

DECTIN-1 expression is higher in AD skin compared to healthy skin. However, stimulation of Dectin-1 expression by Malassezia or IgE crosslinking is impaired in AD-derived mast cells,6 suggesting a defect in defense against fungal infection in AD patients. DECTIN-1 signaling suppresses Th2 immune responses induced by epicutaneous OVA sensitization associated with reduction of IL-4 and IL-13 expression.96 DC-SIGN expression on DCs is high in the lesional skin of AD patients, and the level is associated with disease severity. Zhang et al. suggested that DC-SIGN on DCs binds common allergens such as HDM allergen (Der p 2) and egg white allergen (Gal d2) and initiates allergen sensitization or provokes AD relapse by inducing proinflammatory cytokines including TNF and IL-6 to facilitate Th2 and Th22 polarization.97 On the other hand, Smits et al. showed that DC-SIGN binds *Lactobacillus reuteri* and *Lactobacillus casei*, but not *Lactobacillus plantarum*, driving the differentiation of Treg cells by stimulating monocyte-derived DCs,98 suggesting that targeting of DC-SIGN by certain probiotic bacteria may be beneficial to treat AD.

## 5 | MYELOID CLRS IN TUMOR IMMUNITY

Antitumor immunity is important for protection and eradication of tumors. CLRs are members of the immune surveillance system and are thought to recognize tumor-specific Ags or neo-Ags to activate antitumor immunity. Both acquired immune cells, especially cytotoxic CD8+ T cells (CTLs), and innate immune cells such as NK cells play important roles in the eradication of tumor cells.99,100 On the other hand, Treg cells and myeloid-derived suppressor cells (MDSCs) interfere with the antitumor immunity.101 PD-1/L1 and/or PD-L2 expressed on some tumor cells also inhibit antitumor immunity by interacting with PD-1 on cytotoxic T cells.102 In the course of tumor development, cancer cells frequently metastasize and relocate to other organs through nearby blood vessels. Although CLRs are thought to be involved in these complicated immune processes, their functional roles have not been fully elucidated (Fig. 4).

DECTIN-1 is suggested to play a protective role by directly recognizing tumor-specific Ags. By binding to glycoprotein N-glycans on B16F1 melanoma cells, DECTIN-1 enhances tumor-killing activity of NK cells through induction of INAM and other molecules on DCs and Mfs in an IRF5-dependent manner.103 Furthermore, DECTIN-1 activates Raf1 and NF-κB to express TNFSF15 and OX40L on DCs to promote the differentiation of antitumorigenic Th9 cells.102 DECTIN-1-induced IL-33 also contributes to the induction of Th9 cells.103 DECTIN-1 can also suppress liver inflammation induced by chemical carcinogens, which results in fibrosis and hepatocellular carcinogenesis, by suppressing the expression of TLR4 and CD14 through induction of M-CSF.104 Interestingly, oral administration of yeast-derived β-glucan particles suppresses the growth of subcutaneously inoculated Lewis lung carcinoma, by inducing polymorphonuclear MDSC apoptosis and monocyctic MDSC differentiation to MHC-II+ antitumor APCs through Erk1/2 activation.105 On the other hand, DECTIN-1 expressed on Mfs in mice and humans recognizes the noncanonical DECTIN-1 ligand galectin-9, which is abundantly expressed on pancreatic ductal adenocarcinoma cells, and suppresses M1 Mf differentiation and T cell-mediated antitumor immunity, suggesting a tumor promotive role of DECTIN-1 signaling in pancreatic tumors.106 Furthermore, administration of a DECTIN-1 antagonist, laminarin, to A/Jmrt–deficient mice, a model for spontaneous gastric adenocarcinoma, suppresses gastric dysplasia and attenuates epithelium angiogenesis.107 Therefore, DECTIN-1 plays opposing roles in tumorigenesis depending on the microenvironments of different types of cancers. The precise conditions controlling these functions should be clarified before treatments targeting DECTIN-1 are applied in the clinic.

The genes encoding DECTIN-2, MCL, and MINCLE are mapped in close proximity in the Dectin-2 cluster, and MCL can form heterodimers with DECTIN-2 and MINCLE, implying that these CLRs have related immunological functions even though they recognize distinct ligands. DECTIN-2 and MCL are expressed not only on lymphoid tissues, but also on alveolar Mfs and liver-resident Kupffer cells, which resemble Mfs. Deficiency of either DECTIN-2 or MCL leads to exacerbated liver metastasis after intrasplenic inoculation with SL4 colon carcinoma or B16F1/10 melanoma cells, accompanied by impaired phagocytic activity of Kupffer cells,108 suggesting that these CLRs enhance Kupffer cell-mediated tumor phagocytosis. Similarly, DECTIN-1 deficiency results in severe metastasis of the melanoma cells. In these mice, however, impaired killing activity of nonparenchymal NK cells is suggested to be responsible for the defect of antitumor activity.109 On the other hand, in a pancreatic ductal adenocarcinoma model, MINCLE is up-regulated in tumor-infiltrating Mfs; in addition, by recognizing a subunit of cytoplasmic histone deacetylase complex SAP130, MINCLE promotes oncogenesis by enhancing Mfs-induced immune suppression.109

Expression of CLRs is correlated with development of some human cancers, but the underlying mechanisms remain unknown. Serum levels of soluble DC-SIGN are reduced in colon cancer patients, and high serum levels of soluble DC-SIGN correlate with long-term survival, suggesting that this molecule could serve as a novel prognostic biomarker.110 MICL is detected on acute myeloid leukemia CD34+ stem cells, and mAbs against this molecule cause Ab-dependent cellular cytotoxicity against both cultured and freshly isolated leukemia cells, suggesting a new therapeutic strategy against acute leukemia.111
FIGURE 4 The roles of CLRs in tumor immunity. By suppressing TLR4 and CD14 expression, DECTIN-1 can inhibit inflammation–induced hepatocellular carcinogenesis. β-Glucan stimulation enhances MHC-II+ anti-tumor myeloid–derived cell differentiation through Erk activation to suppress lung carcinoma. DECTIN-1 also activates Raf1 to express TNFSF15 and OX40L to promote anti-tumorigenic Th9 differentiation. Furthermore, by binding to glycoprotein N-glycans on B16 melanoma cells, DECTIN-1 enhances tumor-killing activity of NK cells through IRF5-dependent INAM induction. DECTIN-2 and MCL expressed on liver resident Kupffer cells increase the antitumor phagocytotic activity of these cells. By contrast, DECTIN-1 recognizes noncanonical endogenous ligand galectin-9 expressed on pancreatic cancer cells and suppresses M1 Mϕ-mediated T cell antitumor immunity. In pancreatic ductal adenocarcinoma, MINCLE recognizes the cytoplasmic histone deacetylase complex SAP130 to promote MDSC-mediated immune suppression, thereby down-regulating antitumor immunity.

Recently, the SYK-CARD9 signaling pathway, the common downstream of fungal recognition CLRs such as Dectin-1 or Dectin-2, was shown to be involved in anti-colorectal cancer immunity. Commensal gut fungi activate inflammasomes through the SYK-CARD9 pathway, resulting in the suppression of AOM-DSS–induced colitis and colon tumorigenesis by promoting epithelial barrier restitution via enhancement of IL-18 maturation and IFN-γ production in CD8+ T cells.112 On the other hand, development of AOM-DSS–induced tumors is enhanced in Card9−/− mice, accompanied by an increase in the fungal burden in the intestine, which causes the accumulation of tumor-promoting MDSCs.113 These results suggest that intestinal fungi can either attenuate or promote intestinal tumor development, leaving obscure the exact roles of fungus-induced CLR signaling in the intestinal tumorigenesis.

6 CONCLUDING REMARKS

In this review, we described the roles of myeloid CLRs in diseases of muco-epithelial tissues. Recent progress in research on myeloid CLRs has revealed that in addition to the host defense against pathogens, these molecules play important roles in the homeostasis of
muco-epithelial immunity and development of diseases, including colitis, asthma, psoriasis, atopic dermatitis, and cancers. The functions of these CLRs are complex, and their roles in diseases, their ligands, and the detailed mechanisms underlying their actions remain largely unknown. Elucidation of the physiological as well as pathological roles of these CLRs may provide us with clues that could aid in the development of new therapeutics against these diseases.

AUTHORSHIP
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REFERENCES
1. Cummings RD, McEver RP. C-type lectins. In: Var ki A, Cummings RD, Esko JD, et al., eds. Essentials of Glycobiology. New York, NY: Cold Spring Harbor; 2015:435-452.
2. Drummond RA, Saijo S, Iwakura Y, Brown GD. The role of Syk/CARD9 coupled C-type lectins in antifungal immunity. Eur J Immunol. 2011;41:276-281.
3. Saijo S, Iwakura Y. Dectin-1 and Dectin-2 in innate immunity against fungi. Int Immunol. 2011;23:467-472.
4. Fujikado N, Saijo S, Yonezawa T, et al. Dcir deficiency causes development of autoimmune diseases in mice due to excess expansion of dendritic cells. Nat Med. 2008;14:176-180.
5. Meyer-Wentrup F, Benitez-Ribas D, Tacken PJ, et al. Targeting DCIR on human plasmacytoid dendritic cells results in antigen presentation and inhibits IFN-alpha production. Blood. 2008;111:4245-4253.
6. Meyer-Wentrup F, Cambi A, Joosten B, et al. DCIR is endocytosed into human dendritic cells and inhibits TLR8-mediated cytokine production. J Leukoc Biol. 2009;85:518-525.
7. Treogeler A, Mercier I, Cougoule C, et al. C-type lectin receptor DCIR modulates immunity to tuberculosis by sustaining type I interferon signaling in dendritic cells. Proc Natl Acad Sci USA. 2017;114:E540-E549.
8. Saijo S, Fujikado N, Furuta T, et al. Dectin-1 is required for host defense against Pneumocystis carinii but not against Candida albicans. Nat Immunol. 2007;8:39-46.
9. Saijo S, Ikeda S, Yamabe K, et al. Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation is essential for host defense against Candida albicans. Immunity. 2010;32:681-691.
10. Miyake Y, Toyonaga K, Mori D, et al. C-type lectin MCL is an FcRgamma-coupled receptor that mediates the adhesive activity of mycobacterial cord factor. Immunity. 2013;38:1050-1062.
11. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 2011;34:149-162.
12. Killig M, Glatzer T, Romagnani C. Recognition strategies of group 3 innate lymphoid cells. Front Immunol. 2014;5:142.
13. Hernandez-Santos N, Gaffen SL. Th17 cells in immunity to Candida albicans. Cell Host Microbe. 2012;11:425-435.
14. Yabe R, Iwakura Y, Saijo S. C-Type Lectin Receptors-C-type lectin receptor in host defense against microbial pathogens. In: Taniguchi N, Endo T, Hart G W, Seeberger P H, and Wong C-H, eds. Glycoscience: Biology and Medicine. Tokyo: Japan: Springer; 2015:1319-1329.
15. Bertozzi CC, Schmaier AA, Mericko P, et al. Platelets regulate vascular lymphatic development through CLEC-2-SLP-76 signaling. Blood. 2010;116:661-670.
16. Neumann K, Castineiras-Vilarino M, Hockendorf U, et al. Cic12a is an inhibitory receptor for uric acid crystals that regulates inflammation in response to cell death. Immunity. 2014;40:389-399.
17. Yamasaki S, Ishikawa E, Sakuma M, Hara H, Ogata K, Saito T. Mincl is an ITAM-coupled activating receptor that senses damaged cells. Nat Immunol. 2008;9:1179-1188.
18. Chiba S, Ikushima H, Ueki H, et al. Recognition of tumor cells by Dectin-1 orchestrates innate immune cells for anti-tumor responses. Elife. 2014;3:e04177.
19. Drummond RA, Dambuza IM, Vautier S, et al. CD4(+)- T-cell survival in the GI tract requires dectin-1 during fungal infection. Mucosal Immunol. 2016;9:492-502.
20. Vautier S, Drummond RA, Redelinghuys P, Murray GI, MacCallum DM, Brown GD. Dectin-1 is not required for controlling Candida albicans colonization of the gastrointestinal tract. Infect Immun. 2012;80:4216-4222.
21. Iliev ID, Funari VA, Taylor KD, et al. Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. Science. 2012;336:1314-1317.
22. Tang C, Kamiya T, Liu Y, et al. Inhibition of Dectin-1 signaling ameliorates colitis by inducing Lactobacillus-mediated regulatory T cell expansion in the intestine. Cell Host Microbe. 2015;18:183-197.
23. Kamiya T, Tang C, Kodaki M, et al. beta-Glucans in food modify colonic microflora by inducing antimicrobial protein, calprotectin, in a Dectin-1-induced-IL-17F-dependent manner. Mucosal Immunol. 2018;11:763-773.
24. Shan M, Gentile M, Yeiser JR, et al. Mucus enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals. Science. 2013;342:447-453.
25. Leclaire C, Lecontine K, Gunning PA, et al. Molecular basis for intestinal mucin recognition by galectin-3 and C-type lectins. FASEB J. 2018;32:3301-3320.
26. Lamas B, Richard ML, Leducq V, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Nat Med. 2016;22:598-605.
27. Cohen-Kedar S, Baram L, Elad H, Brazowski E, Guzner-Gur H, Dotan I. Human intestinal epithelial cells respond to beta-glucans via Dectin-1 and Syk. Eur J Immunol. 2014;44:3729-3740.
28. de Vries HS, Plantinga TS, van Krie ken JH, et al. Genetic association analysis of the functional c.714T>G polymorphism and mucosal expression of dectin-1 in inflammatory bowel disease. PLoS One. 2009;4:e7818.
29. Saba K, Denda-Nagai K, Irimura T. A C-type lectin MGL1/CD301a plays an anti-inflammatory role in murine experimental colitis. Am J Pathol. 2009;174:144-152.
30. Hutter J, Eriksson M, Johannsen T, et al. Role of the C-type lectin receptors MCL and DCIR in experimental colitis. PLoS One. 2014;9:e103281.
31. Tokieda S, Komori M, Ishiguro T, Iwakura Y, Takahara K, Inaba K. Dendritic cell immunoreceptor 1 alters neutrophil responses in the development of experimental colitis. BMC Immunol. 2015;16:64.
32. Hayashi S, Sendo M, Hertati A, Tobe K, Kadowaki M. CD206 positive intestinal macrophages contribute to the colonic epithelial wound healing. Cytokine. 2017;100:128-128.
33. Saunders SP, Barlow JL, Walsh CM, et al. C-type lectin SIGN-R1 has a role in experimental colitis and responsiveness to lipopolysaccharide. *J Immunol*. 2010;184:2627-2637.

34. Eriksson M, Johannszen T, von Smolinski D, Gruber AD, Seeberger PH, Lepenies B. The C-Type Lectin receptor SIGNR3 binds to fungi present in commensal microbiota and influences immune regulation in experimental colitis. *Front Immunol*. 2013;4:196.

35. Halwani R, Al-Muhsen S, Hamid Q. Airway remodeling in asthma. *Curr Opin Pharmacol*. 2010;10:236-245.

36. Farahani R, Sherkat R, Hakemi M, Eskandari N, Yazdani R. Cytokines (interleukin-9, IL-17, IL-22, IL-25 and IL-33) and asthma. *Advanced Biomedical Research*. 2014;3:127-127.

37. Lai HY, Rogers DF. Mucus hypersecretion in asthma: intracellular signalling pathways as targets for pharmacotherapy. *Curr Opin Allergy Cl*. 2010;10:67-76.

38. Scherer R, Grayson MH. Heterogeneity and the origins of asthma. *Ann Allergy Asthma Immunol*. 2018;121:400-405.

39. Caminati M, Pham DL, Bagnasco D, Canonica GW. Type 2 immunity in asthma. *World Allergy Organ J*. 2018;11:13.

40. Morishima Y, Ano S, Ishii Y, et al. Th17-associated cytokines as a therapeutic target for steroid-insensitive asthma. *Clin Dev Immunol*. 2013;2013:609395.

41. Trevor JL, Deshane JS. Refractory asthma: mechanisms, targets, and therapy. *Allergy*. 2014;69:817-827.

42. Bozza S, Clavaud C, Giovannini G, et al. Immune sensing of *Aspergillus fumigatus* proteins, glycolipids, and polysaccharides and the impact on Th immunity and vaccination. *J Immunol*. 2009;183:2407-2414.

43. Albacker LA, Chaudhary V, Chang YJ, et al. Invariant natural killer T cells recognize a fungal glycosphingolipid that can induce airway hyperreactivity. *Nat Med*. 2013;19:1297-1304.

44. Ramu S, Menzel M, Bjerner L, Andersson C, Akbarshahi H, Uller L. Allergens produce serine proteases-dependent distinct release of metabolite DAMPs in human bronchial epithelial cells. *Clin Exp Allergy*. 2018;48:156-166.

45. Nakae S, Morita H, Ohno T, Arae K, Matsumoto K, Saito H. Role of interleukin-33 in innate-type immune cells in allergy. *Allergol Int*. 2013;62:13-20.

46. Kurup VP, Xia JQ, Crameri R, et al. Purified recombinant *A. fumigatus* allergens induce different responses in mice. *Clin Immunol*. 2001;98:327-336.

47. Morita H, Arae K, Unno H, et al. An interleukin-33-mast cell-interleukin-2 axis suppresses papain-induced allergic inflammation by promoting regulatory T cell numbers. *Immunity*. 2015;43:175-186.

48. Castanhninha S, Sherburn R, Walker S, et al. Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33. *J Allergy Clin Immunol*. 2015;136:312-322 e7.

49. Sun H, Xu XY, Shao HT, et al. Dectin-2 is predominately macrophage restricted and exhibits conspicuous expression during *Aspergillus fumigatus* invasion in human lung. *Cell Immunol*. 2013;284:60-67.

50. Sun WK, Lu X, Li X, et al. Dectin-1 is inducible and plays a crucial role in *Aspergillus fumigatus*-induced innate immune responses in human bronchial epithelial cells. *Eur J Clin Microbiol Infect Dis*. 2012;31:2755-2764.

51. LeibundGut-Landmann S, Gross O, Robinson MJ, et al. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. *Nat Immunol*. 2007;8:630-638.

52. Robinson MJ, Osorio F, Rosas M, et al. Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. *J Exp Med*. 2009;206:2037-2051.

53. Iwakura Y, Nakae S, Sajio S, Ishigame H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. *Immunol Rev*. 2008;226:57-79.

54. Taylor PR, Roy S, Leal SM, et al. Activation of neutrophils by autocrine IL-17A-IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORgammat and dectin-2. *Nat Immunol*. 2014;15:143-151.

55. Barrett NA, Rahman OM, Fernandez JM, et al. Dectin-2 mediates Th2 immunity through the generation of cysteinyi leukotrienes. *J Exp Med*. 2011;208:593-604.

56. Barrett NA, Maekawa A, Rahman OM, Austen KF, Kanaoka Y, Dectin-2 recognition of house dust mite triggers cysteinyi leukotriene generation by dendritic cells. *J Immunol*. 2009;182:1119-1128.

57. Lilly LM, Gessner MA, Dunaway CW, et al. The beta-glucan receptor dectin-1 promotes lung immunopathology during fungal allergy via IL-22. *J Immunol*. 2012;189:3653-3660.

58. Zhang Z, Biagini Myers JM, Brandt EB, et al. beta-Glucan exacerbates allergic asthma independent of fungal sensitization and promotes steroid-resistant TH2/TH17 responses. *J Allergy Clin Immunol*. 2017;139:54-65 e8.

59. Hadebe S, Kirstein F, Fierens K, et al. Microbial ligand costimulation drives neutrophilic steroid-refractory asthma. *PLoS One*. 2015;10:e0134219.

60. Agarwal R, Chakrabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013;43:850-873.

61. Griffiths JS, Thompson A, Stott M, et al. Differential susceptibility of Dectin-1 isoforms to functional inactivation by neutrophil and fungal proteases. *FASEB J*. 2018;32:3385-3397.

62. Serrano-Gomez D, Domiguez-Soto A, Ancochea J, Jimenez-Hefferman JA, Leal JA, Corbi AL. Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin mediates binding and internalization of *Aspergillus fumigatus* conidia by dendritic cells and macrophages. *J Immunol*. 2004;173:5635-5643.

63. Miller JD. The role of dust mites in allergy. *Clin Rev Allergy Immunol*. 2018.

64. Hadebe S, Brombacher F, Brown GD. C-type lectin receptors in allergy. *Front Immunol*. 2018;9:733.

65. Ito T, Hirose K, Norimoto A, et al. Dectin-1 plays an important role in house dust mite-induced allergic airway inflammation through the activation of CD11b+ dendritic cells. *J Immunol*. 2017;198:61-70.

66. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin FIBCD1 as an acetyl group-binding receptor that binds chitin. *J Immunol*. 2011;208:593-604.

67. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin FIBCD1 as an acetyl group-binding receptor that binds chitin. *J Immunol*. 2011;208:593-604.

68. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin FIBCD1 as an acetyl group-binding receptor that binds chitin. *J Immunol*. 2011;208:593-604.

69. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin FIBCD1 as an acetyl group-binding receptor that binds chitin. *J Immunol*. 2011;208:593-604.

70. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin FIBCD1 as an acetyl group-binding receptor that binds chitin. *J Immunol*. 2011;208:593-604.

71. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin FIBCD1 as an acetyl group-binding receptor that binds chitin. *J Immunol*. 2011;208:593-604.
72. Furmonaviciene R, Ghaemmaghami AM, Boyd SE, et al. The protease allergen Der p 1 cleaves cell surface DC-SIGN and DC-SIGNR: experimental analysis of in silico substrate identification and implications in allergic responses. *Clinical and Experimental Allergy*. 2007;37:231-242.

73. Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. *Autoimmun Rev*. 2014;13:490-495.

74. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. *J Immunol*. 2018;201:1605-1613.

75. Furue K, Ito T, Furue M. Differential efficacy of biologic treatments targeting the TNF-alpha/IL-23/IL-17 axis in psoriasis and psoriatic arthritis. *Cytokeine*. 2018;111:182-188.

76. Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17-producing gamma delta T cells in skin inflammation. *Immunity*. 2011;35:596-610.

77. Woon C, Ober-Blobaum JL, Haak S, et al. Langerin(neg) conventional dendritic cells produce IL-23 to drive psoriatic plaque formation in mice. *Proc Natl Acad Sci U S A*. 2013;110:10723-10728.

78. Pantelyushin S, Haak S, Ingold B, et al. Rorgammam+ innate lymphocytes and gamma delta T cells initiate psoriasisfom plaque formation in mice. *J Clin Invest*. 2012;122:2252-2256.

79. Tortola L, Rosenwald E, Abel B, et al. Psoriasisiform dermatitis is driven by IL-36-mediated DC-keratinocyte crosstalk. *J Clin Invest*. 2012;122:3965-3976.

80. Hashiguchi Y, Yabe R, Chung SH, et al. IL-36alpha from skin-resident dendritic cells produce IL-23 to drive psoriatic plaque formation in mice. *Proc Natl Acad Sci U S A*. 2013;110:10723-10728.

81. Akitsu A, Ishigame H, Kakuta S, et al. IL-1 receptor antagonist-Deficient mice develop autoimmune arthritis due to intrinsic activation of IL-17-producing CCR2(+)Vgamma6(+)gamma delta T cells. *Nat Commun*. 2015;6:7464.

82. Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol*. 2014;32:227-255.

83. Ruutu M, Thomas G, Steck R, et al. beta-glucan triggers spondylarthritosis and Crohn’s disease-like ileitis in SKG mice. *Annu Rev Immunol*. 2015;33:73-96.

84. Yoshitomi H, Sakaguchi N, Kobayashi Y, et al. Role of fungal (beta)glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. *J Exp Med*. 2005;201:949-960.

85. Hashimoto M, Hirota K, Yoshitomi H, et al. Complement drives Th17 cell differentiation and triggers autoimmune arthritis. *J Exp Med*. 2010;207:1135-1143.

86. Wollenberg A, Mommaas M, Oppel T, Schottdorf EM, Gunther S, Moderer M. Expression and function of the mannose receptor CD206 on epidermal dendritic cells in inflammatory skin diseases. *J Invest Dermatol*. 2002;118:327-334.

87. Hagert C, Sareila O, Kelkka T, Jalkanen S, Holmdahl R. The macrophage mannose receptor regulates mannan-induced psoriasis, psoriatic arthritis, and rheumatoid arthritis-like disease models. *Front Immunol*. 2018;9:114.

88. Fuentes-Duculan J, Suarez-Farinas M, Zaba LC, et al. A subpopulation of CD163+ macrophages is classically activated in psoriasis. *J Invest Dermatol*. 2010;130:2412-2422.

89. Srivastava L, Tundup S, Choi BS, Norberg T, Harn D. Immunomodulatory glycan lacto-N-fucopentaose III requires clathrin-mediated endocytosis to induce alternative activation of antigen-presenting cells. *Infect Immun*. 2014;82:1891-1903.

90. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab 66 Suppl*. 2015;1:8-16.

91. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2009;9:437-446.

92. Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The role of malassezia spp. in atopic dermatitis. *J Clin Med*. 2015;4:1217-1228.

93. Scheynius A, Johansson C, Buentke E, Zargari A, Linder MT. Atopic eczema/dermatitis syndrome and Malassezia. *Int Arch Allergy Immunol*. 2002;127:161-169.

94. Yamasaki S, Matsumoto M, Takeuchi O, et al. C-type lectin Mincle is an activating receptor for pathogenic fungus, Malassezia. *Proc Natl Acad Sci U S A*. 2009;106:1897-1902.

95. Ribbing C, Engblom C, Lappalainen J, et al. Mast cells generated from patients with atopic eczema have enhanced levels of granule mediators and an impaired Dectin-1 expression. *Allergy*. 2011;66:110-119.

96. Lin JY, Chen JS, Chen PC, et al. Concurrent exposure to a dectin-1 agonist suppresses the TH2 response to epicutaneously introduced antigen in mice. *J Biomed Sci*. 2013;20:1.

97. Zhang Y, Luo Y, Li W, et al. DC-SIGN promotes allergen uptake and activation of dendritic cells in patients with atopic dermatitis. *J Dermatol Sci*. 2016;84:128-136.

98. Smits HH, Engering A, van der Kleij D, et al. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *J Allergy Clin Immunol*. 2005;115:1260-1267.

99. Borst J, Ahrends T, Babala N, Melief CJM, Kastenmuller W. CD4+(+) T cell help in cancer immunology and immunotherapy. *Nat Rev Immunol*. 2018;18:635-647.

100. Chiossone L, Dumas PY, Vienne M, Vivier E. Natural killer cells and other innate lymphoid cells in cancer. *Nat Rev Immunol*. 2018;18:671-688.

101. Kitamura T, Qian BZ, Pollard JW. Immune cell promotion of metastasis. *Nat Rev Immunol*. 2015;15:73-86.

102. Zhao Y, Chu X, Chen J, et al. Dectin-1-activated dendritic cells trigger potent antitumour immunity through the induction of Th9 cells. *Nat Commun*. 2016;7:12368.

103. Chen J, Zhao Y, Jiang Y, et al. Interleukin-33 contributes to the induction of Th9 cells and antitumor efficacy by dectin-1-activated dendritic cells. *Front Immunol*. 2018;9:1787.

104. Seifert L, Deutsch M, Alothman S, et al. Dectin-1 regulates hepatic fibrosis and hepatocarcinogenesis by suppressing TLR4 signaling pathways. *Cell Rep*. 2015;13:1909-1921.

105. Albeituni SH, Ding C, Liu M, et al. Yeast-derived particulate beta-glucan from brown seaweed-derived beta-glucan effectively restrained peritumoral immune tolerance. *Nat Med*. 2018;24:1285-1292.

106. Daley D, Mani VR, Mohan N, et al. Dectin 1 activation on macrophages by galectin 9 promotes pancreatic carcinoma and peritumoral immune tolerance. *Nat Med*. 2017;23:556-567.

107. Desamero MJ, Kakuta S, Chambers JK, et al. Orally administered brown seaweed-derived beta-glucan effectively restrained development of gastric dysplasia in Agrpnt KO mice that spontaneously develop gastric adenocarcinoma. *Int Immunopharmacol*. 2018;60:211-220.
for the suppression of liver metastasis. *Proc Natl Acad Sci U S A*. 2016;113:14097-14102.

109. Seifert L, Werba G, Tiwari S, et al. The necrosome promotes pancreatic oncogenesis via CXCL1 and Mincle-induced immune suppression. *Nature*. 2016;532:245-249.

110. Jiang Y, Zhang C, Chen K, et al. The clinical significance of DC-SIGN and DC-SIGNR, which are novel markers expressed in human colon cancer. *PLoS One*. 2014;9:e114748.

111. Nonaka M, Imaeda H, Matsumoto S, et al. Mannan-binding protein, a C-type serum lectin, recognizes primary colorectal carcinomas through tumor-associated Lewis glycans. *J Immunol*. 2014;192:1294-1301.

112. Malik A, Sharma D, Malireddi RKS, et al. SYK-CARD9 signaling axis promotes gut fungi-mediated inflammasome activation to restrict colitis and colon cancer. *Immunity*. 2018;49:515-530 e5.

113. Wang T, Fan C, Yao A, et al. The adaptor protein CARD9 protects against colon cancer by restricting mycobiota-mediated expansion of myeloid-derived suppressor cells. *Immunity*. 2018;49:504-514 e4.

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