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

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

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

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

CLRs in anti-fungal immunity
Much of the interest in CLRs has emerged from the discovery that these receptors play critical functions in anti-fungal immunity [8]. In fact our understanding of anti-fungal immunity has significantly increased over the last decade, and we now understand that Th1 effector cells are critical in anti-fungal immunity, particularly from systemic infections with pathogens such as Cryptococcus neoformans [9]. Th17-related immunity, on the other hand, is also critical, being recently demonstrated to be essential for protection at the mucosa [10]. Indeed, defects in several components of the Th17 pathway, from the signalling molecules (CARD9, STAT1, STAT3) to the cytokines involved (IL-17) have been linked to susceptibility to chronic mucocutaneous candidiasis [11]. CLRs, such as Dectin-1 and Dectin-2, play a central role in driving the development of these responses [8]. To date, however, only polymorphisms in Dectin-1 and
mutations in signalling molecule CARD9, which acts downstream of Syk-coupled CLRs (see below), have been linked to susceptibility to fungal infections in humans [12,13].

The study of Dectin-1, in particular, has revolutionised our understanding of host-fungal interactions. This CLR recognises β-glucans, a carbohydrate present in cell walls of many, if not all, fungal species, and is required for immunity to several pathogens including species of Candida, Aspergillus, Pneumocystis and Coccidioides [8]. Dectin-1 was discovered over a decade ago as the first non-Toll-like receptor capable of coupling microbial recognition with gene transcription, and there has been much interest in understanding its intracellular signalling mechanisms [14]. The activation of Dectin-1 requires receptor clustering into a phagocytic synapse [15**], which induces a signalling pathway now known to be common to all the activatory CLRs discussed here: tyrosine phosphorylation of the ITAM-like/ITAM motifs, recruitment and activation of Syk kinase and subsequent activation of the CARD9–Bcl10–Malt1 (CBM) scaffold through PKCθ [16]. Stimulation of this pathway by Dectin-1 and other Syk-independent pathways, such as that mediated by Raf-1, results in the activation of several transcription factors including NFAT, IRF1, IRF5, and the canonical and non-canonical subunits of Nf-κB (p65, RelB, c-Rel, p50 and p52) [6,17–19]. Recently, Dectin-1 activation of CARD9 was shown to regulate H-Ras activation, through Ras-GRF-1 phosphorylation, leading to activation of ERK but not Nf-κB [20] (Figure 2). Dectin-1 mediated signalling can also be suppressed by co-engagement with other CLRs, such as Mincle, which was found to induce Mdm2-dependent loss of nuclear IRF1 activity, blocking Dectin-1 mediated IL-12A transcription [19].

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

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

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**Table 1**

| Alternative names of CLRs discussed in this review |
|---------------------------------------------------|
| CLR mentioned in text | Aliases | Official gene symbol Human/mouse |
|-----------------------|---------|----------------------------------|
| Dectin-1              | CLEC7A, CLECFS12, BGR, CANDF4 | CLEC7A/Clec7a |
| CLEC2                 | CLEC1B, CLEC2B | CLEC1B/Clec1b |
| DNGR-1                | CLEC9A | CLEC9A/Clec9a |
| Dectin-2              | CLEC4A, CLEC6A, CLECFS10, Nicl | CLEC6A/Clec4n |
| CLECSF8               | CLEC4D, CLEC6, MCL, MPCL, Dectin-3 | CLEC4D/Clec4d |
| Mincle               | CLEC4E, CLECFS9 | CLEC4E/Clec4e |
| MICL                 | CLEC12A, CL-1, CL1, DCAL-2, KLRL1 | CLEC12A/Clec12a |

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**Figure 1**

Organisation and orientation of transcription of the genes in the human and mouse ‘Dectin-1’ and ‘Dectin-2’ clusters. ‘Dectin-1’ cluster is in the centromeric part of the human NK gene complex in chromosome 12 (Chr12) and the corresponding region in the mouse is in chromosome 6 (Chr6), while the ‘Dectin-2’ cluster is encoded at the telomeric end of the NK gene complex. Linkage, relative size and orientation of the genes are depicted.
Malassezia [7,30]. Signalling from Dectin-2 induces several responses including the production of cytokines and chemokines [7]. Dectin-2 promotes Th17-biased immunity in response to fungi through the differential activation of cRel containing NF-κB dimers by Malt1, and the preferential induction of IL-23p19 and IL-1β but not IL-12p40 [17]. It is likely that simultaneous engagement with other PRRs is required for amplification of such responses and the recent description of a Dectin-2/CLECSF8 heterodimer with enhanced sensitivity to α-mannans on C. albicans supports this notion [31] (Figure 2). Dectin-2 signalling also augments IL-17RC expression in neutrophils, and is involved in an autocrine IL-17A-IL-17RC feedback loop that is important for ROS production and fungal elimination [32*].

**CLR s in anti-mycobacterial immunity**

In addition to fungi, there is increasing realisation that CLRs play a key role in defence against bacterial infection. CLRs have been implicated in the recognition of several bacterial pathogens [16], but most interest has focused on their role in anti-mycobacterial immunity.
Indeed, several CLRs recognise mycobacteria including Dectin-1, Mincl and most recently CLEC3F8 and Dectin-2 [33–35]. In fact, the activity of Complete Freund’s Adjuvant (CFA), a mycobacterial-based adjuvant widely used in experimental models, was shown to require signalling through Mincl [36]. CLEC3F8, like Mincl, recognises mycobacterial cord factor (trehalose dimycolate, TDM) driving pro-inflammatory innate responses and the development of Th17 immunity [33,34]. CLEC3F8 was also required for induction of Mincl following TDM stimulation [34], leading to the formation of functional heterodimers [37].

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

**CLRs in homeostasis, autoimmunity and allergy**

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

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

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

**CLRs in the recognition of dead cells and tumours**

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

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

Myeloid inhibitory C-type lectin-like receptor (MICL, CLEC3A2, CLL-1) is the newest ‘kid’ on the block and recognises uric acid and proteinaceous ligand(s) on necrotic cells [69*]. MICL functions as an inhibitory receptor, blocking signalling from Syk-coupled activation receptors, and loss of this CLR results in hyperinflammation in the presence of cellular necrosis [69*]. MICL is also highly expressed on most acute myeloid leukaemias and, although its function on these cells is unknown, it has been suggested to be a useful marker of this disease [70].

CLRs have long been associated with immunity to cancer, particularly those receptors expressed on NK cells and involved in the recognition of MHC molecules. Very recently, Dectin-1 has been implicated in NK-mediated killing of tumour cells [71*]. Here, Dectin-1 expressed on DCs and macrophages was shown to recognise N-glycans present on the surface of tumour cells, triggering IRF5 nuclear translocation and induction of several genes including *Il16*, known to enhance tumour killing by NK
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Concluding remarks

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

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest

1. Drickamer K, Fadden AJ: Genomic analysis of C-type lectins. Biochem Soc Symp 2002:59-72.
2. Zelensky AN, Gready JE: The C-type lectin-like domain superfamily. FEBS J 2005, 272:6179-6217.
3. Kerrigan AM, Brown GD: Syk-coupled C-type lectins in immunity. Trends Immunol 2011, 32:151-156.
4. Sancho D, Reis e Sousa C: Signaling by myeloid C-type lectin receptors in immunity and homeostasis. Annu Rev Immunol 2012, 30:491-529.

Comprehensive review of myeloid CLRs and the roles they play in immunity, pathology and homeostasis.

5. Redelinghuys P, Brown GD: Inhibitory C-type lectin receptors in myeloid cells. Immuno Lett 2011, 136:1-12.
6. Plato A, Willment JA, Brown GD: C-type lectin-like receptors of the dectin-1 cluster: ligands and signaling pathways. Int Rev Immunol 2013, 32:134-158.
7. Kerscher B, Willment JA, Brown GD: The Dectin-2 family of C-type lectin-like receptors: an update. Int Rev Immunol 2013, 25: 271-277.
8. Hardison SE, Brown GD: C-type lectin receptors orchestrate antifungal immunity. Nat Immunol 2012, 13:817-822.

9. Wüthrich M, Deepe GS Jr, Klein B: Adaptive immunity to fungi. Annu Rev Immunol 2012, 30:115.
10. Hernández-Santos N, Gaffen Sarah L: Tn17 cells in immunity to Candida albicans. Cell Host Microbe 2012, 11:425-435.
11. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Ohrabieh M, Audry M: Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 2011, 332:65-68.
12. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, Elbers CC, Johnson MD, Cambi A, Huysamen C et al.: Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 2009, 361:1760-1767.
13. Glocke E-O, Hennigs A, Nabavi M, Schäffer AA, Woellner C, Salzer U, Pfeiffer D, Veelken H, Warnatz K, Tahami F: A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 2009, 361:1767-1775.
14. Brown GD, Gordon S: Immune recognition: a new receptor for [beta]-glucans. Nature 2001, 413:36-37.
15. Goodridge HS, Reyes CN, Becker CA, Katsumoto TR, Ma J, Wolf AJ, Bose N, Chan AS, Magee AS, Danielson ME: Activation of the innate immune receptor Dectin-1 upon formation of a ‘phagocytic synapse’. Nature 2011, 472:471-475.

Describes a model mechanism by which innate immune receptors can distinguish direct microbial contact from detection of soluble microbial products.

16. Drummond RA, Brown GD: Signalling C-type lectins in antimicrobial immunity. PLoS Pathog 2013, 9:e1003417.
17. Goodridge HS, Shimada T, Wolf AJ, Hsu Y-MS, Becker CA, Lin X, Underhill DM: Differential use of CARD9 by dectin-1 in macrophages and dendritic cells. J Immunol 2009, 182:1146-1154.
18. Strasser D, Neumann K, Bergmann H, Marakalahla Mohlopheni J, Guler R, Rojowaka A, Hopfner K-P, Brombacher F, URLaub H, Baier G et al.: Syk kinase–coupled C-type lectin receptors engage protein kinase C-5 to elicit CARD9 adaptor-mediated innate immunity. Immunity 2009, 30:39-52.
19. Wevers Brigitte A, Kaptein Tanja M, Zijlstra-Willems Esther M, Theelen B, Boekhout T, Geijtenbeek Teunis BH, Gringhuis Sonja I: Fungal engagement of the C-type lectin melic suppresses dectin-1-induced antifungal immunity. Cell Host Microbe 2014, 15:494-505.
20. Jia X-M, Tang B, Zhu L-L, Liu Y-H, Zhao X-Q, Gorjestani S, Hsu Y-MS, Yang L, Guan J-H, Xu Q-T et al.: CARD9 mediates Dectin-1-induced ERK activation by linking Ras-GRF1 to H-Ras for antifungal immunity. J Exp Med 2014, 211:2307-2321.
21. Ma J, Becker C, Reyes C, Underhill DM: Cutting edge: FTY720 recruitment to dectin-1 phagosomes is accelerated by light chain 3 protein and regulates phagosome maturation and reactive oxygen production. J Immunol 2014, 192:1356-1360.
22. Gringhuis SI, Kaptein TM, Wevers BA, Theelen B, van der Vliet M, Boekhout T, Geijtenbeek TBH: Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1beta via a noncanonical caspase-8 inflammasome. Nat Immunol 2012, 13:246-254.

Describes a new pathway of processing pro-IL-1beta controlled by caspase-8.

23. Hise AG, Tomalka J, Ganesan S, Patel K, Hall BA, Brown GD, Fitzgerald KA: An essential role for the NLRP3 inflammasome in host defense against the human fungal pathogen Candida albicans. Cell Host Microbe 2009, 5:487-497.
24. del Fresno C, Soulat D, Roth S, Blazek K, Udalova I, Sancho D, Fuland J, Ardasiv C, Interferon-beta production via dectin-1-Syk-IRF5 signaling in dendritic cells is crucial for immunity to C. albicans. Immunity 2013, 38:1176-1186.
25. Bourgeois C, Majer O, Frohner IE, Lesiak-Markowicz I, Hildering K-S, Glaser W, Stockinger S, Becker T, Akira S, Müller M: Conventional dendritic cells mount a type I IFN response against Candida spp. requiring novel phagosomal TLR7-mediated IFN-beta signaling. J Immunol 2011, 186:3104-3112.
Innate immunity

26. Smeekens SP, Nij A, Kumar V, Johnson MD, Plantinga TS, van Diemen C, Arts P, Vennema ETM, Greensitt MS, Fransen K et al.: Functional genomics identifies type I interferon pathway as central for host defense against Candida albicans. Nat Commun 2013, 4:1342.

27. Quintin J, Saeed S, Martens JH, Giamarellos-Bourboulis EJ, Ifrim DC, Logie C, Jacobs L, Jansen T, Kullberg BJ, Wijnmenga C et al.: Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes. Cell Host Microbe 2012, 12:233-232.

Identifies a Dectin–1-Raf-1 pathway in epigenetic reprogramming of monocytes as an underlying mechanism of ‘innate memory’.

28. Saeed S, Quintin J, Kerstens HH, Raa NO, Aghajaneirefah A, Matarse F, Cheng S-C, Ratter J, Berentsen K, van der Ent MA: Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. Science 2014, 345:1251086.

29. Ifrim DC, Bain JM, Reid DM, Oosting M, Verschueren I, Gow NA, van Krieken JH, Brown GD, Kullberg B-J, Joosten LA: Role of dectin-2 for host defence against systemic infection with Candida glabrata. Infect Immun 2014, 82:1064–1073.

30. Ishikawa T, Itoh F, Yoshida S, Saijo S, Matsuzawa T, Ganoi O, Saito T, Okawa Y, Shibata N, Miyamoto T et al.: Identification of distinct ligands for the C-type lectin receptors Mincle and Dectin-2 in the pathogenic fungus Malassezia. Cell Host Microbe 2013, 13:477-488.

31. Zhu L-L, Zhao X-Q, Jiang C, You W, Chen X-P, Jiang Y-Y, Jia X-M, Lin X: C-type lectin receptors dectin-3 and dectin-2 form a heterodimeric pattern-recognition receptor for host defense against fungal infection. Immunol 2013, 39:324-334.

32. Taylor PR, Roy S, Leal SM Jr, Sun Y, Howell SJ, Cobb BA, Li X, Pearlman E: Activation of neutrophils by autocrine IL-17A–IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORγt and dectin-2. Nat Immunol 2014, 15:143–151.

Identification of human and mouse neutrophil population with autocrine IL-17 activity controlled, in part, by CLR.

33. Marakalala MJ, Graham LM, Brown GD: The role of Syk/CARD9-coupled C-type lectin receptors in immunity to Mycobacterium tuberculosis infections. Clin Dev Immunol 2011, 2010:567571.

34. Miyake Y, Toyonaga K, Mori D, Kakuta S, Hoshino Y, Oyamada A, Yamada H, Ono K-I, Suyama M, ikawa Y et al.: C-type lectin MCL is an FcγRIIa-coupled receptor that mediates the adjuvanticity of mycobacterial cord factor. Immunity 2013, 38:1050-1062.

35. Yonekawa A, Saijo S, Hoshino Y, Miyake Y, Ishikawa E, Suzukawa M, Inoue H, Tanaka M, Yoneyama M, Oh-hora M: Dectin-2 is a direct receptor for mannose-capped lipopolyborinmannan of mycobacteria. Immunity 2014, 41:402–413.

36. Shenderov K, Barber DL, Mayer-Barber KD, Gurcha SS, Jankovic D, Feng CG, Oland S, Hieny S, Caspar P, Yamashita S: Cord factor and peptidoglycan recapitulate the TH17-promoting adjuvant activity of mycobacteria through mincle/CARD9 signaling and the inflammasome. J Immunol 2015, 190:5722-5730.

37. Lobato-Pascual A, Saetre PC, Fossum S, Dissen E, Daws MR: Mincle, the receptor for mycobacterial cord factor, forms a functional receptor complex with MCL and FcRi-γ. Eur J Immunol 2013, 43:3167-3174.

38. Heittmann L, Schoenhen H, Ehlers S, Lang R, Hölscher C: Mincle is not essential for controlling Mycobacterium tuberculosis infection. Immunobiology 2013, 218:508-516.

39. Behler F, Steinewede K, Balboa L, Ueberberg B, Mahu R, Kirchhof G, Yamazaki S, Wilse T, Maus U: Role of Mincle in alveolar macrophage-dependent innate immunity against mycobacterial infections in mice. J Immunol 2012, 189:3121-3129.

40. Lee W-B, Kang J-S, Yan J-J, Lee MS, Jeon B-Y, Cho S-N, Kim Y-J: Neutrophils promote mycobacterial trehalose dimycolate-induced lung inflammation via the Mincle pathway. PLoS Pathog 2012, 8:e1002614.

41. Dorhoe A, Desel C, Yeremeev V, Pradi L, Brinkmann V, Mollenkopf H-J, Hawke D, Gross O, Ruland J, Kaufmann SH: The adaptor molecule CARD9 is essential for tuberculosis control. J Exp Med 2010, 207:777-792.

Identifies CARD9 as an essential signaling molecule in antymycobacterial immunity.

42. Karumuthil-Melethil S, Gudi R, Johnson BM, Perez N, Vasu C: Fungal β-glucan, a dectin-1 ligand, promotes protection from type 1 diabetes by inducing regulatory innate immune response. J Immunol 2014, 193:3308-3321.

43. Yoshitomi H, Sakaguchi N, Kobayashi K, Brown GD, Tagami T, Sakahama T, Hirota K, Tanaka S, Nomura M, Miki I: A role for fungal β-glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. J Exp Med 2005, 201:949-960.

44. Karsten CM, Pandey MK, Figge J, Kilchenstein R, Taylor PR, Rosas M, McDonald JU, Orr SJ, Berger M, Petzold D et al.: Anti-inflammatory activity of IgG1 mediated by Fc galactosylation and association of Fc(γ)RIIB and dectin-1. Nat Med 2012, 18:1401-1406.

45. Acton SE, Astarita JL, Mahotra D, Lukacs-Kornek V, Franz B, Hess PR, Jakus Z, Kuligowski M, Fletcher AL, Elpek KG: Podoplanin-rich stromal networks induce dendritic cell motility via activation of the C-type lectin receptor CLEC-2. Immunity 2012, 37:276-289.

46. Bénêzech C, Nayar S, Finney BA, Withers DR, Lowe K, Desanti GE, Marriott CL, Watson SP, Caamaño JH, Buckley CD: CLEC-2 is required for development and maintenance of lymph nodes. Blood 2014, 123:3200-3207.

47. Bertozzi CC, Schmaier AA, Mericco P, Hess PR, Zou Z, Chen M, Chen CY, Xu B, Lu MM, Zhou D: Platelets regulate lymphatic vascular development through CLEC-2–SLP-76 signaling. Blood 2010, 116:661-670.

48. Herzog BH, FJ, Wilson SJ, Hess PR, Sen A, McDaniel JM, Pan Y, Sheng M, Yago T, Silasi-Mansat R: Podoplanin maintains high endothelial venule integrity by interacting with platelet CLEC-2. Nature 2013, 202:105-109.

49. Rochereau N, Drocourt D, Perouzel E, Pevor V, Redlinghuys P, Brown GD, Tiraby G, Roblin X, Verrier B, Genin C: Dectin-1 is essential for reverse transcytosis of glycosylated SlgA–antigen complexes by intestinal M cells. PLoS Biol 2013, 11:e1001658.

50. Shan M, Gentile M, Yeier JR, Wallard AC, Bornstein VJ, Chen K, He B, Cassis L, Bigas A, Cols M: Mucus enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals. Science 2013, 342:447-453.

Describes the role of glycans associated with MUC2 in regulation of mucosal tolerance to commensal bacteria. MUC2 constrains the immunomodulatory gut antigens through assembly of a galectin–Dectin-1–Fc-Ryβ receptor complex that activates β-catenin and inhibits nuclear factor κB.

51. Iliiev ID, Funari VA, Taylor KD, Nguyen Q, Reyes CN, Strom SP, Brown J, Becker CA, Fleschner PR, Dubinsky M: Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. Science 2012, 336:1314-1317.

Shows that Dectin-1 limits inflammation induced by fungi following mucosal damage in the gut.

52. Lilly LM, Gessner MA, Dunaway CW, Metz AE, Schwiebert L, Weaver CT, Brown GD, Steele C: The β-glucan receptor dectin-1 promotes lung immunopathology during fungal allergy via IL-22. J Immunol 2012, 189:3563-3560.

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

54. Barrett NA, Rahman OM, Fernandez JM, Parsons MW, Xing W, Austen KF, Kanaoka Y: Dectin-2 mediates Th2 immunity through the generation of cysteinyloleukotrienes. J Exp Med 2011, 208:593-604.

55. Clarke DL, Davis NHE, Campion CL, Foster ML, Heasman SC, Lewis AR, Anderson IK, Corkill DJ, Sleeiman MA, May RD et al.: Dectin-2 sensing of house dust mite is critical for the initiation of airway inflammation. Mucosal Immunol 2014, 7:558-567.
56. Tipta MY, Hrusch CL, Blaine KM, Williams JW, Barnett NA. Sperling AI: Signaling through FcyRy-associated receptors on dendritic cells drives IL-33-dependent TH2-type responses. J Allergy Clin Immunol 2014, 134:706–713.e708.

57. Parsons MW, Li L, Wallace AM, Lee MJ, Katz HR, Fernandez JM, Saijo S, Iwakura Y, Austen KF, Kanaoka Y et al.: Dectin-2 regulates the effector phase of house dust mite-elicted pulmonary inflammation independently from its role in sensitization. J Immunol 2014, 192:1361–1371.

58. Norimoto A, Hirose K, Iwata A, Tamachi T, Yokota M, Takahashi K, Saijo S, Iwakura Y, Nakajima H: Dectin-2 promotes house dust mite-induced T helper type 2 and type 17 cell differentiation and allergic airway inflammation in mice. Am J Respir Cell Mol Biol 2014, 51:201-209.

59. Sancho D, Reis e Sousa C: Sensing of cell death by myeloid C-type lectin receptors. Curr Opin Immunol 2013, 25:46-52.

60. Yamasaki S, Ishikawa E, Sakuma M, Hara H, Ogata K, Saito T: Mincle is an ITAM-coupled activating receptor that senses damaged cells. Nat Immunol 2008, 9:1179-1186.

61. Suzuki Y, Nakano Y, Mishiro K, Takagi T, Tsuruma K, Nakamura M, Yoshimura S, Shimazawa M, Hara H: Involvement of Mincle and Syk in the changes to innate immunity after ischemic stroke. Sci Rep 2013, 3:3177.

62. de Rivera Vaccari JC, Frank Brand I, Bert AF, Alonso OF, Bullock R, De Rivera Vaccari JP: Mincle signaling in the innate immune response after traumatic brain injury. J Neurotrauma 2014 http://dx.doi.org/10.1089/jn.2013.3436.

63. Schraml BU, van Blijswijk J, Zelenay S, Whitney PG, Filby A, Acton SE, Rogers NC, Moncaut N, Carvajal JJ, Reis e Sousa C: Genetic tracing via DNGR-1 expression history defines dendritic cells as a hematopoietic lineage. Cell 2013, 154:843-858.

64. Ahrens S, Zelenay S, Sancho D, Hanč P, Kjaer S, Feest C, Fletcher G, Durkin C, Postigo A, Skehel M et al.: F-actin is an evolutionarily conserved damage-associated molecular pattern recognized by DNGR-1, a receptor for dead cells. Immunity 2012, 36:635-645. See ref. [65].

65. Zhang J-G, Czabotar Peter E, Policeni Antonia N, Caminschi I, San Wan S, Kitsoulis S, Tullet Kirsteen M, Robin Adeline Y, Brammananth R, van Delft Mark F et al.: The dendritic cell receptor Clec9A binds damaged cells via exposed actin filaments. Immunity 2012, 36:646-657. Together with [64*], identify F-actin as the ligand for DNGR-1.

66. Sancho D, Joffre OP, Keller AM, Rogers NC, Martinez D, Harnaz-Falcon P, Rosewell I, Reis e Sousa C: Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. Nature 2008, 458:899-903.

Identifies DNGR-1 as a CLR that senses necrotic cells and is involved in regulating cross-presentation of cell-associated antigens.

67. Iborra S, Izquierdo HM, Martinez-López M, Blanco-Menéndez N, Reis e Sousa C. Sancho D: The DC receptor DNGR-1 mediates cross-priming of CTLs during vaccinia virus infection in mice. J Clin Invest 2012, 122:1628-1643.

68. Zelenay S, Keller AM, Whitney PG, Schraml BU, Dedouche S, Rogers NC, Schulz O, Sancho D, Reis e Sousa C: The dendritic cell receptor DNGR-1 controls endocytic handling of necrotic cell antigens to favor cross-priming of CTLs in virus-infected mice. J Clin Invest 2012, 122:1615-1627.

69. Neumann K, Castañeras-Vilarinho M, Höckendorf U, Hannesschläger N, Lemeer S, Kupka D, Meyermann S, Lech M, Anders H-J, Kuster B et al.: Clec12a is an inhibitory receptor for uric acid crystals that regulates inflammation in response to cell death. Immunity 2014, 40:389-399. Identifies a negative regulator of sterile inflammation to cell death that has implications for autoimmunity and inflammatory diseases.

70. Roug AS, Larsen HØ, Nederby L, Just T, Brown G, Nyvold CØ, Omnen HB, Hokland P, hMCL and CD123 in combination with a CD45/CD34/CD117 backbone — a universal marker combination for the detection of minimal residual disease in acute myeloid leukaemia. Br J Haematol 2014, 164:212-222.

71. Chiha S, Ikushima H, Ueki H, Yanai H, Kimura Y, Hangai S, Nishijo J, Negishi H, Tamura T, Saijo S: Recognition of tumor cells by Dectin-1 orchestrates innate immune cells for anti-tumor responses. eLife 2014 http://dx.doi.org/10.7554/eLife.04177. Dectin-1 is identified as a receptor that facilitates the identification of cancer associated ligands and signalling cascades that enhances tumouricidal activity of NK cells.

72. Brown GD, Gordon S: Fungal β-glucans and mammalian immunity. Immunity 2003, 19:311-315.

73. Sattler S, Ghadially H, Hofer E: Evolution of the C-type lectin-like receptor gene of the DECTIN-1 cluster in the NK gene complex. Sci World J 2012, 2012:931386.