

## RESEARCH HIGHLIGHT

## Dectin-1 in the control of Th2-type T cell responses

Katherine Upchurch<sup>1,2</sup>, SangKon Oh<sup>1,2</sup>, HyeMee Joo<sup>1,2</sup>

<sup>1</sup>Baylor Institute for Immunology Research, Dallas, TX 75204, USA

<sup>2</sup>Baylor University, Institute for Biomedical Studies, Waco, TX 76706, USA

Correspondence: HyeMee Joo

E-mail: [hyemee.joo@baylorhealth.edu](mailto:hyemee.joo@baylorhealth.edu)

Received: November 02, 2015

Published online: January 04, 2016

Dendritic cells (DCs) are major antigen-presenting cells (APCs) that can induce and control host immune responses. DCs express pattern recognition receptors (PRRs), which can translate external and internal triggers into different types of T cell responses. The types of CD4<sup>+</sup> T cell responses elicited by DCs (e.g., Th1, Th2, Th17, Th21, Th22 and regulatory T cells (Tregs)) are associated with either host immunity or inflammatory diseases, including allergic diseases and autoimmune diseases. In particular, the pathogenic functions of Th2-type T cells in allergic immune disorders have been well documented, although Th2-type T cell responses are crucial for immunity against certain parasite infections. Recent evidence also indicates that the inflammatory Th2 signatures in cancers, including breast and pancreatic cancers, are highly associated with poor clinical outcomes in patients. It is thus important to find cellular/molecular targets expressed in DCs that control such inflammatory Th2-type T cell responses. In a recent paper published in *The Journal of Immunology*, we demonstrated that Dectin-1 expressed on the two major human DC subsets, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), has opposing roles in the control of Th2-type CD4<sup>+</sup> T cell responses. Dectin-1 expressed on mDCs decreases Th2-type CD4<sup>+</sup> T cell responses, while Dectin-1 expressed on pDCs favors Th2-type CD4<sup>+</sup> T cell responses. This finding expands our understanding of the roles of DCs and Dectin-1 expressed on DCs in the pathogenesis of Th2-associated diseases and in host immunity to microbial infections and cancers.

**To cite this article:** Katherine Upchurch, et al. Dectin-1 in the control of Th2-type T cell responses. *Receptor Clin Invest* 2016; 3: e1094. doi: 10.14800/rci.1094.

**Copyright:** © 2016 The Authors. Licensed under a *Creative Commons Attribution 4.0 International License* which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

DCs are major antigen-presenting cells (APCs) that can efficiently induce and activate host immune responses. DCs are also able to control immune responses towards immunity or tolerance <sup>[1, 2]</sup>, partly due to their ability to control the types of antigen-specific CD4<sup>+</sup> T cell responses. Such functional plasticity of DCs for the control of the quality and magnitudes of T cell responses is largely dependent on activation signals delivered through a variety of pattern recognition receptors (PRRs), including TLRs, retinoic acid-inducible gene 1 (RIG-I)-like receptors,

nucleotide-binding oligomerization domain receptors (NOD-like receptors) and C-type lectin receptors. Recent studies have shown that PRR-mediated activation of other cell types, particularly cells surrounding DCs in tissue environments, can also promote functional plasticity of DCs to control the type of CD4<sup>+</sup> T cell responses.

Dectin-1, a C-type lectin receptor, is known to be expressed on myeloid DCs (mDCs) <sup>[3, 4]</sup> but not plasmacytoid DCs (pDCs) <sup>[5, 6]</sup> in humans. It delivers intracellular signals

and activates DCs, resulting in the initiation of immune responses [3, 7-9]. After recognition of  $\beta$ -glucans [10], the tyrosine residue within the cytoplasmic immunoreceptor tyrosine-based activation marker (ITAM) motif is phosphorylated [11, 12], followed by the recruitment of spleen tyrosine kinase (Syk) and caspase recruitment domain-containing protein 9 (CARD9) [13-20]. Such sequential signaling cascades give rise to the activation of nuclear factor of activated T cells (NFAT) [21], mitogen-activated protein kinase (MAPK) [22] and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) [12, 13, 23, 24]. The activation of Dectin-1 signaling pathways can thus lead to the release of cytokines [3], including IL-10, IL-6, TNF $\alpha$ , and IL-23 [14, 23]. These cytokines can directly influence the quality of T cell responses and, in particular, Dectin-1-mediated DC activation promotes Th17 cell differentiation [3, 14, 25, 26]. In accordance, human memory T cell responses to fungal antigens are mainly Th17- [13, 14], with a lesser involvement of Th1-type T cell responses [27, 28]. Cytokines, such as IL-6 and IL-1 $\beta$ , released by Dectin-1-activated antigen-presenting cells (APCs) enhance the induction and activation of IL-17-producing T cell responses [13, 14, 19, 29], which are essential for host defense against certain fungal and bacterial infections [13, 14, 30, 31].

Dectin-1 contains an internalization signal sequence for the lysosomal endosome [32, 33] and thus phagocytosis of  $\beta$ -glucan particles by Dectin-1 can contribute to antigen-specific T cell responses. Recently, Carter *et al.* [26] showed that ovalbumin (OVA)-transgenic mice immunized with OVA conjugated anti-Dectin-1 antibody induced potent CD4<sup>+</sup> T cell responses, but weak CD8<sup>+</sup> T cell responses. On the other hand, Leibundgut-Landmann *et al.* [34] showed that murine DCs stimulated with  $\beta$ -glucans were able to prime cytotoxic CD8<sup>+</sup> T cell responses. These studies suggested that Dectin-1 mediated antigen delivery could result in both antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses. Consistently, in our recent study, we showed that antigen targeting to human DCs via Dectin-1 results in antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses [19, 35]. In addition, we demonstrated that antigen targeting to DCs via human Dectin-1 (hDectin-1) along with TLR2 ligands could promote antigen-specific Th17 responses in humans [19]. In line with these observations,  $\beta$ -glucans, as well as an agonistic anti-hDectin-1 antibody, can activate DCs to produce multiple cytokines, including IL-6, IL-1 $\beta$ , and IL-10 [9, 35, 36, 37, 38].

In humans, Dectin-1 is expressed not only on mDCs and macrophages, but also on B cells, neutrophils, and eosinophils [4], suggesting that Dectin-1 expression in humans is not myeloid restricted. Therefore, we re-investigated hDectin-1 expression and function on pDCs

and compared them with those of mDCs [38]. In contrast to previous reports [5, 6], we found that pDCs from the blood of healthy individuals express Dectin-1, although the surface expression levels of Dectin-1 on pDCs from blood, tonsils, and spleens were not similar. We also found that the expression levels of surface Dectin-1 on pDCs from the blood were highly variable among healthy subjects, suggesting that Dectin-1 expression on human pDCs could be controlled by factors that need to be further characterized. Dectin-1 expression in human pDCs was further confirmed at the RNA level, where we determined two major isoforms (A and B) and one minor isoform (D) of Dectin-1 in pDCs. We further reported that Dectin-1 expressed on pDCs could deliver activation signals via Syk, resulting in pDC surface maturation as well as cytokine (IL-6, TNF $\alpha$ , and IFN $\alpha$ ) and chemokine (IP-10, MIP-1 $\alpha$ , MIP-1 $\beta$ , and IL-8) expression. Unlike mDCs stimulated with house dust mite *Dermatophagoides farinae* (Df) via Dectin-2, pDCs stimulated with  $\beta$ -glucan did not secrete cysteinyl leukotrienes (Cys-LT), which has been associated with Th2 immunity to inhaled allergens [39]. Instead, pDCs activated via Dectin-1 expressed IFN $\alpha$ , which can induce the expression of OX40L that in turn promotes Th2-type T cell responses. This clearly illustrates that pDCs have unique functions to promote Th2 responses, particularly in the presence of Dectin-1 ligands.

OX40 ligand (OX40L) is known to be mainly expressed by APCs, although it is not constitutively expressed. It can also be induced in various other cell types, including endothelial cells and T cells [40, 41]. The receptor for OX40L, OX40, is mainly found on activated CD4<sup>+</sup> and CD8<sup>+</sup> T cells. When expressed alongside a co-stimulatory molecule on APCs, OX40L is able to prolong T cell survival and increase T cell cytokine production [41]. One of the most well defined modulations of OX40L expression on DCs is through thymic stromal lymphopoietin (TSLP). TSLP is a cytokine produced by epithelial cells, especially those in the lung, skin and gut, but also may be produced by fibroblasts, smooth muscle cells and mast cells [42, 43]. TSLP-treated mDCs express high levels of CD86, a co-stimulatory marker, as well as OX40L. When these TSLP-DCs are co-cultured with CD4<sup>+</sup> T cells, the T cells give rise to inflammatory Th2 cells, producing high levels of IL-4, IL-5, IL-13, and TNF $\alpha$  [43-45].

In contrast to the roles of Dectin-1 expressed on human pDCs, mDCs activated via Dectin-1 significantly decrease Th2-type CD4<sup>+</sup> T cell responses [38]. This applies to both induction and activation of naïve and memory CD4<sup>+</sup> T cell responses. We further demonstrated that Dectin-1-activated mDCs secrete IL-10, which contributes to the suppression of OX40L expression. This is followed by decreased Th2-type T cell responses [38]. Such contrasting roles of Dectin-1

expressed on the two major subsets of human DCs might have important implications in inflammatory Th2-associated allergic immune disorders as well as in certain types of cancers, although further studies need to be performed in the context of such diseases. Meanwhile, data from our study [38] suggest that Dectin-1 expressed on mDCs could be a novel target to suppress the induction as well as activation of such inflammatory Th2-type T cell responses.

### Conflict of interests

The authors have declared that no conflict of interests exists.

### Acknowledgments

This work was supported by the NIH (1R21AI101810-01) and Baylor Health Care System Foundation.

### Abbreviations

APC: antigen-presenting cell; BDCA-2: blood dendritic cell antigen-2; CARD9: caspase recruitment domain-containing protein 9; Cys-LT: cysteinyl leukotriene; DC: dendritic cell; hDectin-1: human Dectin-1; IFN: interferon; IL: interleukin; ITAM: immunoreceptor tyrosine-based activation motif; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; mDC: myeloid DC; MHC: major histocompatibility complex; NFAT: nuclear factor of activated T cells; NF- $\kappa$ B: nuclear factor kappa-light-chain-enhancer of activated B cells; NOD: nucleotide-binding oligomerization domain; OVA: ovalbumin; OX40L: OX40 ligand; PAMP: pathogen associated molecular pattern; pDC: plasmacytoid DC; PRR: pattern recognition receptor; RIG-1: retinoic-acid-inducible protein 1; RNA: ribonucleic acid; Syk: spleen tyrosine kinase; TLR: toll-like receptor; TNF $\alpha$ : tumor necrosis factor  $\alpha$ ; TSLP: thymic stromal lymphopoietin.

### References

1. Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003; 21:685-711.
2. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature* 1998; 392:245-252.
3. Brown GD. Dectin-1: a signalling non-TLR pattern-recognition receptor. *Nat Rev Immunol* 2006; 6:33-43.
4. Taylor PR, Brown GD, Reid DM, Willment JA, Martinez-Pomares L, Gordon S, et al. The beta-glucan receptor, dectin-1, is predominantly expressed on the surface of cells of the monocyte/macrophage and neutrophil lineages. *J Immunol* 2002; 169:3876-3882.
5. Meyer-Wentrup F, Benitez-Ribas D, Tacke PJ, Punt CJ, Figdor CG, de Vries IJ, et al. Targeting DCIR on human plasmacytoid

- dendritic cells results in antigen presentation and inhibits IFN-alpha production. *Blood* 2008; 111:4245-4253.
6. Willment JA, Marshall AS, Reid DM, Williams DL, Wong SY, Gordon S, et al. The human beta-glucan receptor is widely expressed and functionally equivalent to murine Dectin-1 on primary cells. *Eur J Immunol* 2005; 35:1539-1547.
7. Taylor PR, Tsoni SV, Willment JA, Dennehy KM, Rosas M, Findon H, et al. Dectin-1 is required for beta-glucan recognition and control of fungal infection. *Nat Immunol* 2007; 8:31-38.
8. Rothfuchs AG, Bafica A, Feng CG, Egen JG, Williams DL, Brown GD, et al. Dectin-1 interaction with Mycobacterium tuberculosis leads to enhanced IL-12p40 production by splenic dendritic cells. *J Immunol* 2007; 179:3463-3471.
9. Drummond RA, Brown GD. The role of Dectin-1 in the host defence against fungal infections. *Curr Opin Microbiol* 2011; 14:392-399.
10. Rahar S, Swami G, Nagpal N, Nagpal MA, Singh GS. Preparation, characterization, and biological properties of beta-glucans. *J Adv Pharm Technol Res* 2011; 2:94-103.
11. Herre J, Marshall AS, Caron E, Edwards AD, Williams DL, Schweighoffer E, et al. Dectin-1 uses novel mechanisms for yeast phagocytosis in macrophages. *Blood* 2004; 104:4038-4045.
12. Rogers NC, Slack EC, Edwards AD, Nolte MA, Schulz O, Schweighoffer E, et al. Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. *Immunity* 2005; 22:507-517.
13. Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, et al. Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature* 2006; 442:651-656.
14. Leibundgut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, 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.
15. Hara H, Ishihara C, Takeuchi A, Imanishi T, Xue L, Morris SW, et al. The adaptor protein CARD9 is essential for the activation of myeloid cells through ITAM-associated and Toll-like receptors. *Nat Immunol* 2007; 8:619-629.
16. Goodridge HS, Shimada T, Wolf AJ, Hsu YM, Becker CA, Lin X, et al. Differential use of CARD9 by dectin-1 in macrophages and dendritic cells. *J Immunol* 2009; 182:1146-1154.
17. Gantner BN, Simmons RM, Canavera SJ, Akira S, Underhill DM. Collaborative induction of inflammatory responses by dectin-1 and Toll-like receptor 2. *J Exp Med* 2003; 197:1107-1117.
18. Brown GD, Herre J, Williams DL, Willment JA, Marshall AS, Gordon S. Dectin-1 mediates the biological effects of beta-glucans. *J Exp Med* 2003; 197:1119-1124.
19. Duluc D, Joo H, Ni L, Yin W, Upchurch K, Li D, et al. Induction and activation of human Th17 by targeting antigens to dendritic cells via dectin-1. *J Immunol* 2014; 192:5776-5788.
20. Carmona EM, Vassallo R, Vuk-Pavlovic Z, Standing JE, Kottom TJ, Limper AH. Pneumocystis cell wall beta-glucans induce dendritic cell costimulatory molecule expression and inflammatory activation through a Fas-Fas ligand mechanism. *J Immunol* 2006; 177:459-467.
21. Goodridge HS, Simmons RM, Underhill DM. Dectin-1 stimulation by Candida albicans yeast or zymosan triggers NFAT activation in macrophages and dendritic cells. *J Immunol* 2007;

- 178:3107-3115.
22. Dillon S, Agrawal S, Banerjee K, Letterio J, Denning TL, Oswald-Richter K, *et al.* Yeast zymosan, a stimulus for TLR2 and dectin-1, induces regulatory antigen-presenting cells and immunological tolerance. *J Clin Invest* 2006; 116:916-928.
  23. Dennehy KM, Ferwerda G, Faro-Trindade I, Pysz E, Willment JA, Taylor PR, *et al.* Syk kinase is required for collaborative cytokine production induced through Dectin-1 and Toll-like receptors. *Eur J Immunol* 2008; 38:500-506.
  24. Slack EC, Robinson MJ, Hernanz-Falcon P, Brown GD, Williams DL, Schweighoffer E, *et al.* Syk-dependent ERK activation regulates IL-2 and IL-10 production by DC stimulated with zymosan. *Eur J Immunol* 2007; 37:1600-1612.
  25. Weck MM, Appel S, Werth D, Sinzger C, Bringmann A, Grunebach F, *et al.* hDectin-1 is involved in uptake and cross-presentation of cellular antigens. *Blood* 2008; 111:4264-4272.
  26. Carter RW, Thompson C, Reid DM, Wong SY, Tough DF. Preferential induction of CD4+ T cell responses through in vivo targeting of antigen to dendritic cell-associated C-type lectin-1. *J Immunol* 2006; 177:2276-2284.
  27. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, *et al.* Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol* 2007; 8:639-646.
  28. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, *et al.* Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 2000; 13:715-725.
  29. Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat Immunol* 2007; 8:942-949.
  30. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cilley GE, *et al.* IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during Mycobacterium tuberculosis challenge. *Nat Immunol* 2007; 8:369-377.
  31. Lin Y, Ritchea S, Logar A, Slight S, Messmer M, Rangel-Moreno J, *et al.* Interleukin-17 is required for T helper 1 cell immunity and host resistance to the intracellular pathogen Francisella tularensis. *Immunity* 2009; 31:799-810.
  32. Ariizumi K, Shen GL, Shikano S, Xu S, Ritter R, 3rd, Kumamoto T, *et al.* Identification of a novel, dendritic cell-associated molecule, dectin-1, by subtractive cDNA cloning. *J Biol Chem* 2000; 275:20157-20167.
  33. Engering A, Geijtenbeek TB, van Vliet SJ, Wijers M, van Liempt E, Demaurex N, *et al.* The dendritic cell-specific adhesion receptor DC-SIGN internalizes antigen for presentation to T cells. *J Immunol* 2002; 168:2118-2126.
  34. Leibundgut-Landmann S, Osorio F, Brown GD, Reis e Sousa C. Stimulation of dendritic cells via the dectin-1/Syk pathway allows priming of cytotoxic T-cell responses. *Blood* 2008; 112:4971-4980.
  35. Ni L, Gayet I, Zurawski S, Duluc D, Flamar AL, Li XH, *et al.* Concomitant activation and antigen uptake via human dectin-1 results in potent antigen-specific CD8+ T cell responses. *J Immunol* 2010; 185:3504-3513.
  36. Goodridge HS, Wolf AJ, Underhill DM. Beta-glucan recognition by the innate immune system. *Immunol Rev* 2009; 230:38-50.
  37. LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, *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.
  38. Joo H, Upchurch K, Zhang W, Ni L, Li D, Xue Y, *et al.* Opposing Roles of Dectin-1 Expressed on Human Plasmacytoid Dendritic Cells and Myeloid Dendritic Cells in Th2 Polarization. *J Immunol* 2015; 195:1723-1731.
  39. Barrett NA, Rahman OM, Fernandez JM, Parsons MW, Xing W, Austen KF, *et al.* Dectin-2 mediates Th2 immunity through the generation of cysteinyl leukotrienes. *J Exp Med* 2011; 208:593-604.
  40. Wang YH, Liu YJ. OX40-OX40L interactions: a promising therapeutic target for allergic diseases? *J Clin Invest* 2007; 117:3655-3657.
  41. Croft M, So T, Duan W, Soroosh P. The significance of OX40 and OX40L to T-cell biology and immune disease. *Immunol Rev* 2009; 229:173-191.
  42. Liu YJ, Soumelis V, Watanabe N, Ito T, Wang YH, Malefyt Rde W, *et al.* TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu Rev Immunol* 2007; 25:193-219.
  43. Liu YJ. Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell-mediated allergic inflammation. *J Allergy Clin Immunol* 2007; 120:238-244.
  44. Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N, *et al.* TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med* 2005; 202:1213-1223.
  45. Lambrecht BN, Hammad H. Lung dendritic cells in respiratory viral infection and asthma: from protection to immunopathology. *Annu Rev Immunol* 2012; 30:243-270.