CORRESPONDENCE

Pulmonary CD103+ dendritic cells: key regulators of immunity against infection

Sudhanshu Shekhar[1] and Xi Yang[2]

Cellular & Molecular Immunology (2020) 17:670–671; https://doi.org/10.1038/s41423-020-0397-8

Since the discovery of dendritic cells (DCs) by the Nobel laureate Professor Ralph Steinman et al. in 1973, a plethora of literature has accumulated on the functional roles of DCs in humans and animal models.[1] DCs are involved in the innate sensing and modulation of adaptive immunity to pathogens. CD103+ DCs constitute a classical nonlymphoid DC subset that has an important role in generating immunity and maintaining tolerance.[2] Pulmonary CD103+ DCs (CD103+ PDCs), which reside in close association with the airway epithelium, are particularly critical in controlling T-cell immunity against lung infections.[2,3] In this article, we discuss recent evidence that shines light on the role and mechanism of CD103+ PDCs in modulating CD8+ and CD4+ T-cell responses against various pathogens, including bacteria and viruses. A deeper understanding of CD103+ PDC function may provide new translational avenues for the development of vaccines and therapeutics against infectious diseases.

Mouse CD103+ PDCs are phenotypically characterized by the expression of α_E(CD103)β_7, CD11c^{hi}, CD207, MHC-II, TLR3, XCR1, and Clec9a/DNGR1 but not CD64 and CD11b.[3] The transcription factors Batf3 and Irf8 are critical for the development of CD103+ PDCs, as shown by the lack of these DCs in Batf3- or Irf8-deficient mice.[3] Following pulmonary infection, CD103+ PDCs upregulate costimulatory molecules (CD40, CD80, and CD86), produce large quantities of several cytokines (IL-4, IL-13, IL-12, IL-10, IL-23, and IL-6), migrate to the lung-draining mediastinal lymph nodes, and prime naive CD4+ and CD8+ T cells to induce antigen-specific immune responses.[4–6] Recent studies indicate that CD103+ DCs, along with lymphoid CD8α+ DCs, form a new class of DCs referred to as type 1 DCs (DC1s), which express the chemokine receptor XCR1 and perform the unique function of cross-presenting exogenous antigens with MHC-I molecules to CD8+ T cells.[7] Owing to similar phenotypic and functional characteristics, human CD141/BDCA-3+ DCs are considered equivalent to murine DC1s.[8] Overall, these DCs constitute a unified DC subset in mice and humans that is developmentally and functionally related.

An accumulating wealth of evidence stemming from mouse studies has focused on the function of CD103+ PDCs during viral and bacterial infections.[4,6,9] Upon challenge with respiratory influenza A virus or poxvirus infection, mice that lack CD103+ DCs, such as Batf3$^{-/-}$ and Clec9A− diphtheria toxin receptor transgenic mice, failed to induce protective immunity, in contrast to control mice, suggesting a protective role for CD103+ PDCs in viral infections.[6,9,10] Following influenza A virus infection, CD103+ PDCs acquired and processed apoptotic cell-associated viral antigens in their endocytic compartment, migrated to the mediastinal lymph nodes, and cross-presented the antigens on MHC-I molecules to naive CD8+ T cells to elicit protective virus-specific cytotoxic responses.[6,11] Interestingly, CD103+ PDCs could cross-present antigens from virally infected cells because of their ability to resist infection by influenza virus via a type I interferon-mediated antiviral state.[6] On the other hand, ablation of CD103+ PDCs resulted in decreased production of IFN-γ by CD8+ T cells and reduced expression of the activation and transcription markers Ki67, CD25, and T-bet in these cells after respiratory vaccinia virus infection.[10] Liang Ng et al.[12] have further shown that CD103+ PDCs not only control cross-priming of CD8+ T cells but also regulate their migration, viability, and memory responses during influenza infection. In doing so, CD103+ PDCs induce upregulated levels of sphingosine-1-phosphate receptor, which is important for egress of lymphocytes from the lymph nodes, on activated CD8+ T cells[12]. Moreover, adoptive transfer of bone marrow-derived CD103+ DCs in CD103+ DC-ablated mice promoted the survival of virus-specific effector CD8+ T cells.[12] In addition, CD103+ PDCs purified from the lungs of influenza virus-infected mice expressed an enhanced level of IL-15, which is a critical cytokine for the maintenance of naive and memory T cells.[12] Thus, CD103+ PDCs occupy a central position in regulating various aspects of CD8+ T-cell responses against viral infections.

Hemann et al.[13] recently elucidated the immune mechanism that directs CD103+ PDCs to modulate antiviral CD8+ T-cell immunity. Mice lacking the receptor (Ifnlr1$^{-/-}$) of type III interferon (IFN-λ), which is an immune-modulatory cytokine that has the ability to promote CD8+ T-cell immunity against influenza A virus, showed a significant reduction in migratory CD103+ PDCs, along with CD8α+ DCs, in the mediastinal lymph nodes after influenza A virus infection.[13] Furthermore, specific deletion of IFN-λ receptor 1 in CD11c+ DCs in a conditional knockout mouse model mirrored the global immune phenotype of Ifnlr1$^{-/-}$ mice, particularly the diminished CD8+ T-cell responses.[13] Taken together, these findings indicate that IFN-λ signaling has an important role in programming CD103+ PDCs for migration from the lungs to the lymph nodes and induction of an optimal CD8+ T-cell response against influenza A virus. Provided the importance of the CD103+ PDC-IFN-λ-CD8+ T-cell axis in adaptive immunity, it may be prudent to exploit IFN-λ as a vaccine adjuvant against influenza infection.

Most information on how CD103+ PDCs control CD4+ T-cell responses comes from studies using bacterial and fungal pathogens.[4,5,14,15] Analysis of CD103+ PDCs from *Klebsiella pneumoniae*-infected mice showed that the PDCs imparted enhanced antigen-specific CD4+ T-cell responses in an in vitro

[1]Institute of Oral Biology, University of Oslo, Oslo, Norway and [2]Department of Immunology, University of Manitoba, Winnipeg, Canada
Correspondence: Xi Yang (x.yang@umanitoba.ca)

Received: 25 February 2020 Accepted: 26 February 2020
Published online: 17 March 2020

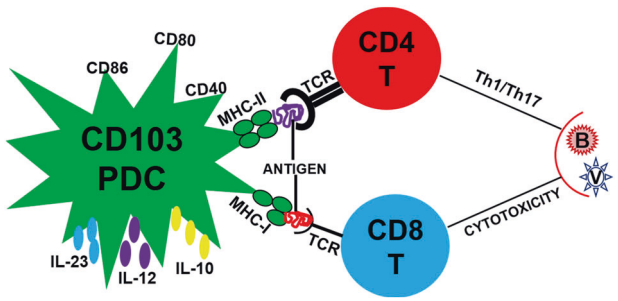

Fig. 1 CD103+ PDC-mediated T-cell responses to pathogens. Following a respiratory infection with pathogens, CD103+ PDCs acquire and process microbial antigens, express costimulatory molecules (e.g., CD80, CD86, and CD40), secrete multiple cytokines (e.g., IL-23, IL-12, and IL-10), and migrate to the lung-draining lymph nodes to present the antigens on MHC-I/MHC-II molecules to the TCR of naive CD8+/CD4+ T cells, inducing cytotoxic/T helper (Th1/17) responses against viral and bacterial pathogens. *PDC* pulmonary dendritic cell, *IL* Interleukin, *MHC* major histocompatibility complex, *TCR* T-cell receptor, *B* bacterium, *V* virus

DC-T-cell coculture system with OVA TCR transgenic CD4+ T helper cells.[5] Recently, we assessed the immune function of classical major PDC subsets, CD103+ and CD11b^{hi} PDCs, in a mouse model of pulmonary chlamydial infection.[4] Intranasal transfer of CD103+ PDCs isolated from *Chlamydia muridarum*-infected mice into naive mice induced better protection against *C. muridarum* challenge infection than that in CD11b^{hi} PDC recipients.[4] Analysis of cytokines in CD103+ PDC recipients clearly showed a stronger bias toward Th1 (IFN- γ) and Th17 (IL-17) responses than that in mice receiving CD11b^{hi} PDCs. These data suggest a predominant role for the CD103+ PDC subset over CD11b^{hi} PDCs in conferring protective Th1/Th17 immunity to chlamydial infection. In accordance with these findings, depletion of CD103+ PDCs in mice resulted in increased bacterial burdens in the lungs and lymph nodes following *Mycobacterium tuberculosis* infection, which was associated with consistently reduced levels of total and activated CD4+ and CD8+ T cells and Th1-related cytokines (IFN-γ and TNF-α).[14] Using a mouse model of pulmonary *Aspergillus fumigatus* infection, Zelante et al.[15] deciphered the mechanisms by which CD103+ PDCs control CD4+ cell function in the lungs. *A. fumigatus* triggers CD103+ PDCs to secrete IL-2 through the receptor dectin-1, phagocytosis, and Ca^{2+}-calmodulin-dependent NFAT signaling pathway, thus eliciting IL-17+ CD4+ T-cell responses that induce protective immunity.[15] On the other hand, CD103+ PDCs incompetent for IL-2 production produce IL-23, which in turn causes lethal Th17-driven hyperinflammation.[15] In summary, the equilibrium between CD103+ PDC-expressed IL-2 and IL-23 is critical for modulating mucosal pulmonary responses to infection.

CD103+ PDCs are critical to adaptive immunity against pulmonary infections. They not only excel in cross-priming CD8+ T cells to generate antigen-specific cytotoxic responses against viruses but also induce effective CD4+ T-cell immunity (Th1/Th17) to bacterial and fungal pathogens (Fig. 1). Indeed, a multifaceted role for CD103+ PDCs in pathogen defense is becoming clearer in light of new knowledge originating from various mouse studies. The indispensability of CD103+ PDCs for the generation and maintenance of protective antiviral T cells suggests that vaccination strategies should target these DCs to achieve optimal immunity. Modulation of CD103+ PDC function may have implications for both ensuing protective immunity and suppressing infection-driven hyperinflammation in the lungs. The relevance of data accumulated regarding murine CD103+ PDCs for humans warrants further exploration. The similarity of human CD141+ DCs to murine CD103+ DCs presents an opportunity to establish a functional correlation between these two DC subsets in mice and humans during infection. Moving in this direction, humanized mice have emerged as an attractive model to study CD141+ DC function in vivo under naive and infectious conditions. This advance is owing mainly to the striking functional similarities of CD141+ DCs from humanized mice, such as cross-priming and IFN-λ expression, with those found in the human blood.[16]

AUTHOR CONTRIBUTIONS

SS and XY wrote the manuscript and gave approval of its last version to be published.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

REFERENCES

1. Steinman, R. M. & Cohn, Z. A. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J. Exp. Med.* **137**, 1142–1162 (1973).
2. del Rio, M. L., Bernhardt, G., Rodriguez-Barbosa, J. I. & Forster, R. Development and functional specialization of CD103+ dendritic cells. *Immunol. Rev.* **234**, 268–281 (2010).
3. Kessel, C. H. G. & Lambrecht, B. N. Division of labor between dendritic cell subsets of the lung. *Mucosal Immunol.* **1**, 442–450 (2008).
4. Shekhar, S., Peng, Y., Wang, S. & Yang, X. CD103+ lung dendritic cells (LDCs) induce stronger Th1/Th17 immunity to a bacterial lung infection than CD11b(hi) LDCs. *Cell Mol. Immunol.* **15**, 377–87. (2018).
5. Hackstein, H. et al. Modulation of respiratory dendritic cells during Klebsiella pneumonia infection. *Resp. Res.* **14**, 91 (2013).
6. Helft, J. et al. Cross-presenting CD103(+) dendritic cells are protected from influenza virus infection. *J. Clin. Invest.* **122**, 4037–4047 (2012).
7. Gutierrez-Martinez, E. et al. Cross-presentation of cell-associated antigens by MHC class I in dendritic cell subsets. *Front. Immunol.* **6**, 363 (2015).
8. O'Keeffe, M., Mok, W. H. & Radford, K. J. Human dendritic cell subsets and function in health and disease. *Cell. Mol. Life Sci.* **72**, 4309–4325 (2015).
9. GeurtsvanKessel, C. H. et al. Clearance of influenza virus from the lung depends on migratory langerin(+)CD11b(−) but not plasmacytoid dendritic cells. *J. Exp. Med.* **205**, 1621–34. (2008).
10. Desai, P., Tahiliani, V., Abboud, G., Stanfield, J. & Salek-Ardakani, S. Batf3-dependent dendritic cells promote optimal CD8 T cell responses against respiratory poxvirus infection. *J. Virol.* **92**, e00495–18 (2018).
11. Ho, A. W. et al. Lung CD103+ dendritic cells efficiently transport influenza virus to the lymph node and load viral antigen onto MHC class I for presentation to CD8 T cells. *J. Immunol.* **187**, 6011–6021 (2011).
12. Ng, S. L., Teo, Y. J., Setiagani, Y. A., Karjalainen, K. & Ruedl, C. Type 1 conventional CD103(+) dendritic cells control effector CD8(+) T cell migration, survival, and memory responses during influenza infection. *Front. Immunol.* **9**, 3043 (2018).
13. Hemann, E. A. et al. Interferon-lambda modulates dendritic cells to facilitate T cell immunity during infection with influenza A virus. *Nat. Immunol.* **20**, 1035–45. (2019).
14. Koh, V. H. et al. Role and contribution of pulmonary CD103(+) dendritic cells in the adaptive immune response to Mycobacterium tuberculosis. *Tuberculosis (Edinb.)* **102**, 34–46 (2017).
15. Zelante, T. et al. CD103(+) dendritic cells control Th17 cell function in the lung. *Cell Rep.* **12**, 1789–1801 (2015).
16. Minoda, Y. et al. Human CD141(+) dendritic cell and CD1c(+) dendritic cell undergo concordant early genetic programming after activation in humanized mice in vivo. *Front Immunol.* **8**, 1419 (2017).