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RESEARCH HIGHLIGHT

Proinflammatory IL-17 induces iBALT development

Mingzhao Zhu[1] and Yangxin Fu[2]

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The development of secondary lymphoid organs (SLOs) and tertiary lymphoid organs (TLOs) share many common mechanisms. Molecules of the tumor necrosis factor family, especially lymphotoxin, and the lymphoid homeostatic chemokines, such as CXCL13, CCL19 and CCL21, play important roles in the development of both SLOs and TLOs.[1–3] This may be unsurprising given the common microarchitectural features of SLOs and TLOs.

However, the processes of SLO and TLO development differ markedly. Whereas SLOs are usually embryonically programmed in the lymphoid anlagen under steady state conditions, TLOs are often reprogrammed postnatally in non-lymphoid tissues under chronic inflammatory conditions. Given these temporal and spatial differences and the differences in microenvironmental influences, the cellular and molecular components involved in the development of TLOs and SLOs could differ considerably. Unraveling the distinct features of TLOs and SLOs and the mechanisms by which they are formed have become topics of great interest in the field.

Inducible bronchus-associated lymphoid tissue (iBALT) is a TLO that forms in the lungs in response to local infection or during chronic pulmonary inflammation. A previous study by the same research group demonstrated that iBALT can form independently of lymphotoxin after influenza virus infection, leaving open the intriguing question of what drives iBALT formation.[4] In the current study, Randall *et al.* have revealed an unexpected and novel role for IL-17 in the initiation of iBALT.[5]

The authors first attempted to induce iBALT by repeatedly administering Lipopolysaccharide (LPS) intranasally, but this protocol failed. Surprisingly, the same protocol resulted in typical iBALT formation in neonatal mice, and this iBALT persisted into adulthood. The temporal difference led the authors to investigate the role of LTi cells, which are more prevalent in neonatal mice than in adult mice. However, the possibility that LTi cells are involved in iBALT formation was conclusively ruled out using RORgt-deficient mice and Id-2-deficient mice, which cannot develop LTi cells.

A careful examination of the gene expression pattern in neonatal and adult pulmonary tissue after exposure to LPS revealed that IL-23p19 and IL-17A are induced in neonates but not in adults. The importance of IL-17A and IL-23 was confirmed using IL-17A-deficient mice and IL-23p19-deficient mice.

Why is IL-17 important? IL-17, also known as IL-17A, functions as a potent proinflammatory cytokine in airway inflammation during the invasion of bacteria, viruses and fungi.[6,7] IL-17 exerts its activity by upregulating the expression of chemokines, cell adhesion molecules and cytokines in a range of cells, including airway epithelial cells, fibroblasts and smooth muscle cells.[6,7] Given the inflammatory feature of TLOs compared with SLOs, it is not unexpected that an inflammatory mechanism underlies the development of TLOs. In the current study, the authors provide the first example linking inflammatory IL-17 to the development of iBALT.

The cellular source of IL-17 during iBALT formation remains unclear, although it seems highly likely that $CD4^+$ T cells are involved. It is interesting that although γδ−T cells produce more IL-17 than αβ−T cells, αβ−T cells seem to be more important for the development of iBALT, according to the T-cell adoptive transfer experiment conducted by Randall et al. Do these two T-cell subsets have different roles in iBALT formation? It is possible that γδ−T cells initiate the formation of iBALT through IL-17, whereas αβ−T cells promote iBALT growth and maintenance independently of IL-17, through lymphotoxin (Figure 1). This model is supported by the following findings. First, γδ−T cells are innate immune cells and therefore can quickly respond to foreign stimuli, whereas it takes at least several days for αβ−T cells to differentiate into IL-17 producing Th17 cells. Thus, γδ−T cells, and not αβ−T cells, are the major IL-17 producer during early, innate, immune responses.[7] A time-course study of the IL-17 producing cells after treatment with LPS would help to clarify this issue. Second, lymphotoxin was found to be important for the maintenance of iBALT in the current study. One important cellular source of lymphotoxin is αβ-T cells. We cannot, however, rule out the potential role of B cell-derived lymphotoxin in iBALT maintenance, given the importance of this source of lymphotoxin during SLO development. These intriguing questions are worthy of further study using TCRβ or TCRδ single-deficient mice and lymphotoxin conditional knockout mice.

The current study also poses interesting questions about whether this mechanism holds true for iBALT formation during adulthood and during inflammation induced by other stimuli. As Cupedo[8] noted, the immune systems of neonatal and adult mice differ in their responsiveness, and these mice have different exposures to commensal microbes. In addition to the differences mentioned above, stromal cell properties might also be critical. Lymphoid organizer cells are stromal cells that form the architecture of lymphoid organs. Embryonic mesenchymal cells are considered to be the stromal organizer cells in SLO development.[9] It has been unclear which stromal cell type, such as mesenchymal cells, epithelial cells, fibroblasts, endothelial cells and smooth muscle cells, is

[1]Key Laboratory of Infection and Immunity, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China and [2]Department of Pathology and Committee on Immunology, The University of Chicago, Chicago, IL, USA
Correspondence: Dr MZ Zhu, Key Laboratory of Infection and Immunity, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China.
E-mail: zhumz@ibp.ac.cn
or Dr YX Fu, Department of Pathology and Committee on Immunology, The University of Chicago, Chicago, IL 60637, USA.
E-mail: yxfu@bsd.uchicago.edu
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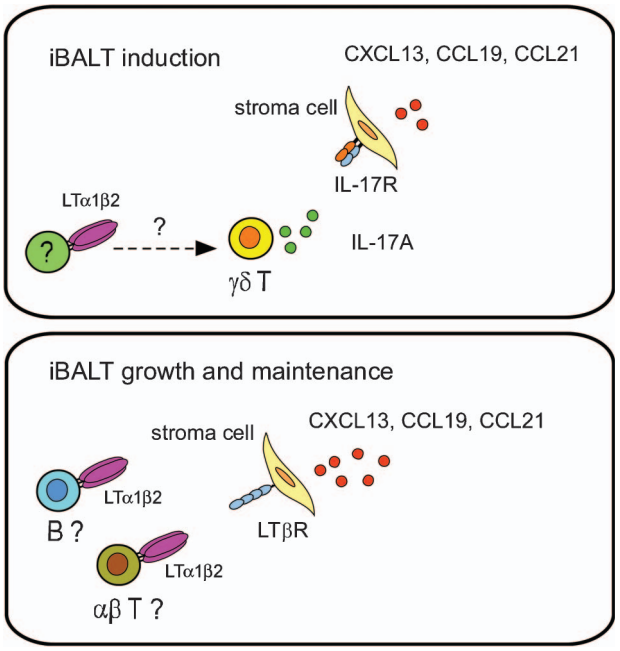

Figure 1 Orchestrated regulation of iBALT development by lymphotoxin and IL-17A. Both IL-17A and lymphotoxin play important roles in the formation of iBALT. γδ-T cells could be the major cellular source of IL-17A at the early stage of inflammation, and lymphotoxin from an unknown cell source might regulate γδ-T cell migration or production of IL-17A. IL-17A upregulates the expression of lymphoid chemokines through binding to its receptor IL-17R on stromal cells. At the stage of iBALT growth and maintenance, lymphotoxin, not IL-17A, is the major signal that stimulates further lymphoid chemokine expression by stromal cells. αβ-T cells or B cells may be the cellular source of lymphotoxin, an interesting issue that remains to be determined. iBALT, inducible bronchus-associated lymphoid tissue.

the organizer cell in TLO development.[9] But it is likely that the stromal components differ between embryos, neonates and adults. These points remain to be tested in future studies. The authors also noticed different Th17 development in the gut of the same strain of mice but at two different institutes, and they suggest that gut flora might be a determining factor. It will therefore also be important to determine definitively whether respiratory tract flora are the crucial players.

Similarly to other conditions under which TLOs and SLOs develop, the lymphotoxin pathway is required for iBALT development upon repeated stimulation with LPS.[1,9] It is intriguing that the lymphotoxin and IL-17 pathways are both involved in the early stages of iBALT formation. The lymphotoxin pathway was recently found to be important for innate immune responses in the gut epithelium during *Citrobacter rodentium* infection.[10,11] The production of IL-22, another IL-17 family cytokine, by innate lymphoid cells, was positively regulated by lymphotoxin signaling. Is it possible that IL-17 production by γδ−T cells at the early stage of iBALT formation is also regulated by lymphotoxin? This remains an interesting open question.

The current study has unraveled a unique mechanism for TLO development that differs from SLO development. As discussed above, SLOs and TLOs differ in many aspects. In addition, the unique properties of various non-lymphoid tissues may influence TLO development in these tissues. The study by Randall *et al.* has opened new avenues and raised many interesting questions that await future studies.

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