Rangel-Moreno *et al.* reply:

We thank Fleige *et al.* for their comments about the role of IL-17 in the formation of iBALT. They have presented data showing that both CXCL13 expression and iBALT formation can occur independently of IL-17A and IL-17F after infection with MVA. Thus, they conclude that IL-17 is not required for either iBALT formation or CXCL13 expression in the lungs. In contrast, our data have shown that repeated pulmonary administration of LPS to neonatal mice promotes iBALT formation and that this process is dependent on both IL-17R and IL-17A[1]. We also found that the blockade of IL-17 with a neutralizing antibody to IL-17 resulted in smaller B cell follicles (**Fig. 1a**,**b**) and FDC networks (**Fig. 1c**) and fewer follicles (**Fig. 1d**). Given that we obtained similar results after pulmonary aerosol infection with *Mycobacterium tuberculosis* (unpublished data), we feel confidant that the IL-17 pathway is important for iBALT formation in our experiments.

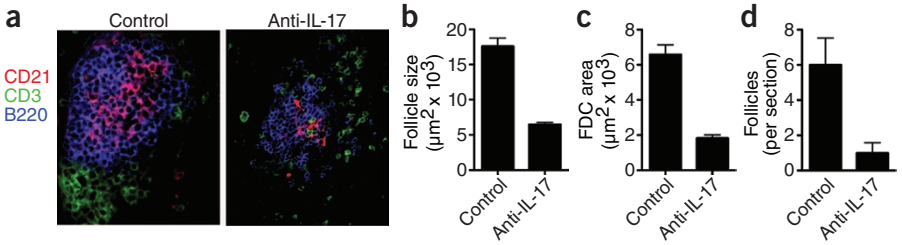

Figure 1 Blockade of IL-17 disrupts iBALT formation. (**a**) Frozen sections of lungs from neonatal mice ($n = 5$ per group) given 10 μg LPS intranasally five times (once every other day starting on day 2 after birth) and treated intranasally with anti-IL-17 (MAB421; R&D Systems) or 25 μg isotype-matched control antibody (02-9688; Zymed) 1 d before the final administration of LPS; lung sections obtained 1 week after the final LPS administration were stained with anti-CD21-CD35 (7E9; BioLegend), anti-CD3 (M-20; Santa Cruz Biotechnology) and anti-B220 (RA3-6B2; BD Biosciences). (**b**,**c**) Area of B cell follicles (**b**) and follicular dendritic cell (FDC) networks (**c**) in the mice in **a**, determined with the outline tool of Axiovision software (Zeiss). (**d**) Follicles in sections from the mice in **a**, determined by counting of stained sections. Data are representative of two independent experiments (mean and s.e.m. in **b**–**d**).

Nevertheless, the data presented by Fleige *et al.* have shown that iBALT can form independently of IL-17A and IL-17F under some circumstances. For our model, we propose that LPS triggers acute production of IL-23 and IL-17, which leads to early inducible expression of CXCL13 in the lung. In turn, CXCL13 initiates iBALT formation by recruiting CXCR5-expressing B cells and follicular helper T cells (T_{FH} cells). CXCL13 is also inducibly expressed in the lung after influenza infection[2] and is most probably expressed after MVA infection. Whereas CXCL13 expression after acute exposure to LPS is dependent on IL-17, the results of Fleige *et al.* suggest that the acute induction of CXCL13 after viral infection probably uses other pathways. In contrast, we have found that once iBALT is formed and inflammation has resolved, the structure of iBALT is maintained via the homeostatic expression of CXCL13 and lymphotoxin and not IL-17 (ref. 1). Thus, we are not at all surprised that Fleige *et al.* found normal CXCL13 expression in IL-17-deficient mice that had already formed iBALT.

The formation of ectopic follicles also correlates with responses of the T_H17 subset of helper T cells in a variety of diseases, including infection with bacteria, such as *Helicobacter pylori*[3] or *Mycobacterium tuberculosis*[4], as well as in some autoimmune diseases, such as rheumatoid arthritis[5] and multiple sclerosis[6]. In contrast, acute viral infections typically lead to type 1 helper T responses (T_H1 responses) and the production of type I interferon. Although type I interferon can have a negative effect on IL-17 production[7], it also promotes T_{FH} differentiation[8]. Given our data showing that IL-17-expressing T_{FH} cells are more efficient at promoting iBALT formation than are conventional T_H17 cells[1], it is possible that MVA infection elicits another type of T_{FH} cell that promotes iBALT independently of IL-17.

Another notable difference between our data and those of Fleige *et al.* is that we have never observed iBALT formation in adult C57BL/6 mice after pulmonary infection with influenza virus or other viruses[1]. Given that both Fleige *et al.* and we have used C57BL/6 mice, the most probable explanation for the differences in our results is the environment. In fact, differences in food, bedding or commensal colonization of the gut can have substantial consequences for immunological outcomes[9,10], particularly those associated with inflammatory diseases. Similarly, differences in commensal colonization may alter the number or repertoire of regulatory T cells, which are also known to affect the formation of iBALT[11].

In summary, the results of Fleige *et al.* have clearly demonstrated that ectopic follicles such as iBALT can form independently of IL-17 in response to some types of inflammatory triggers. Nevertheless, we stand by our data showing that IL-17 is essential for iBALT formation in response to LPS-mediated inflammation, and we believe that IL-17-mediated induction of CXCL13 expression is a common mechanism for the formation of ectopic follicles in response to bacterial infection as well as in a variety of autoimmune and inflammatory diseases.

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COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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