B cells and T follicular helper-like cells within lung granulomas are required for TB control

We show a crucial protective function for T follicular helper (T_{FH})-like cells localized within granuloma-associated lymphoid tissue for *Mycobacterium tuberculosis* control in mouse models of tuberculosis. Antigen-specific B cells contribute to this strategic localization and the maturation of cytokine-producing T_{FH}-like cells.

This is a summary of:
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The question

Tuberculosis (TB) is primarily a lung infection caused by the intracellular pathogen *Mycobacterium tuberculosis* (*Mtb*). TB exists as a spectrum of disease, from latent TB infection and subclinical disease to active TB, with variable clinical outcomes potentially linked with the lung immune landscape[1] and granulomas, a hallmark of TB. A granuloma is a collection of immune cells (including B cells and T cells) recruited to the site of infection to contain *Mtb* proliferation; an organized granuloma-associated lymphoid tissue (GrALT) comprises well-defined lymphoid follicles localized near or within TB granulomas, orchestrates optimal interactions between lymphocytes and is associated with *Mtb* control[2,3] and latent TB infection[4]. However, the molecular interactions that generate efficient pulmonary immunity during TB are unknown. We designed this study to delineate the specific T cell and B cell protective functions within the GrALT that mediate *Mtb* control.

The discovery

IRF4, which encodes the crucial transcription factor interferon regulatory factor 4 that is required for B cell and T cell differentiation, is downregulated during progression to active TB in humans and animal models of TB[1]. We used mouse models with conditional deletion of *Irf4* in T cells and B cells ($Cd4^{cre}Irf4^{fl/fl}$ mice that lacked T helper 1 (T_H1), T_H17 and T_{FH}-like cells, and $Cd19^{cre}Irf4^{fl/fl}$ mice that lacked germinal center B cells, respectively), and we show that *Irf4* expression in T cells is essential to support GrALT formation and *Mtb* control (measured as lung bacterial load). $IRF4^+$ T cells co-express B cell lymphoma 6 protein (BCL6) during *Mtb* infection. *Bcl6* deficiency in T cells ($Cd4^{cre}Bcl6^{fl/fl}$ mice lacking T_{FH}-like cells) but not in B cells ($Cd19^{cre}Bcl6^{fl/fl}$ mice lacking germinal center B cells) prevents GrALT formation and *Mtb* control. In addition, *Mtb*-specific B cells are needed for *Mtb* control and GrALT formation in mouse and macaque models. In mice, we show that important B cell effector mechanisms, such as antibody production (as shown in $Cd19^{cre}Blimp1^{fl/fl}$ mice, which lack the BLIMP1 transcription factor required for plasma cell differentiation), antigen presentation (as observed in $Cd19^{cre}iAB^{fl/fl}$ mice, which lack the beta component of the major histocompatibility complex class 2), or germinal center B cells (in $Cd19^{cre}Bcl6^{fl/fl}$ mice) are not required for either control of *Mtb* or GrALT formation. Upon *Mtb* infection, levels of programmed cell death 1 ligand 1 (PD-L1) were increased in B cells, and the interaction of PD-L1 with its receptor programmed cell death protein 1 (PD-1) expressed on lung T_{FH}-like cells was required to enhance the differentiation from pre-T_{FH}-like cells to mature T_{FH}-like cells and localize T_{FH} cells within GrALT to mediate *Mtb* control (Fig. 1). Mice that lack *Mtb*-specific B cells (IghelMD4 mice) failed to do so. Thus, our results reveal a crucial protective function for T_{FH}-like cells localized within GrALT, and support the contribution of B cells in the strategic localization of cytokine-producing T_{FH}-like cells within the GrALT for *Mtb* control.

The implications

We show a crucial contribution of the transcription factors IRF4 and BCL6 in $CD4^+$ T cells in the generation of cytokine-producing T_{FH}-like cells, which localize within GrALT to mediate *Mtb* control. Our results suggest that *Mtb*-specific B cells are needed to orchestrate T_{FH}-like cell differentiation and accumulation in the GrALT, induce cytokine production via PD-L1–PD-1 engagement, and influence GrALT organization. Altogether, these results answer long-standing questions about the contribution of T_{FH}-like cells and B cells in the generation of a protective GrALT involved in the generation of local immunity to control *Mtb* infection.

Although our study does not show a direct protective role for antibody-producing or antigen-presenting B cells in lung *Mtb* control, it is possible that these B cell effector mechanisms function to control TB dissemination. We hope that this research will provide targets and immune pathways to improve the design of TB vaccines.

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EXPERT OPINION

"This is an exciting, well-developed, and important study for the field of TB immunology. Understanding the intricate relationships between protective and detrimental immune responses in the lung is of critical importance for understanding *Mycobacterium tuberculosis* pathogenesis and TB vaccine development. More broadly, the mechanistic relationships between B cells, T_{FH}-like cells and GrALT formation described in this study could have implications for other diseases." **Andreas Kupz, James Cook University, Cairns, Australia.**

FIGURE

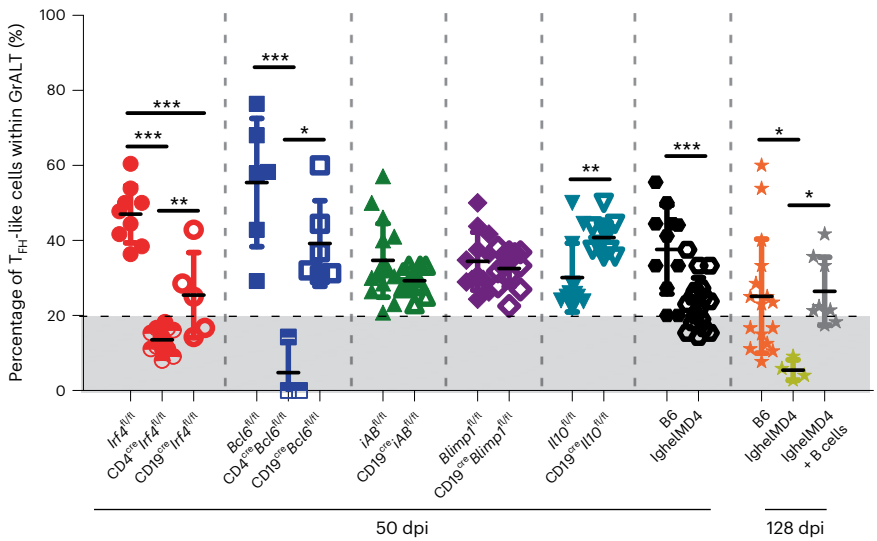

Fig. 1 | T_{FH}-like cells localize within GrALT for *Mtb* control. Mice were infected with *Mtb*, and their lungs were collected at 50 or 128 days post infection (dpi). Lung sections were immune-labelled and analyzed for the percentage of PD-1$^+$CD3$^+$ T_{FH}-like cells within B cell areas. Data are mean ± s.d. B6, wild-type mice strain. $^*P \le 0.05$; $^{**}P \le 0.005$; $^{***}P \le 0.0005$. © 2023, Swanson, R. V. et al.

BEHIND THE PAPER

For the past decade, we have been interested in understanding the protective function of T cells and B cells within GrALT. To mechanistically address this question, we generated the various mouse models described in this paper and systematically addressed the specific role of T_{FH}-like cells and B cell function in mediating *Mtb* control. An important but surprising turning point for the paper came from the experiments that showed that it was not the size of GrALT, but instead a certain threshold abundance of T_{FH}-like cells localized within GrALT that correlated with protection against *Mtb*. This study took about five years from conception to completion, and one additional year of work will hopefully enable us to refine the targets of the T cell–B cell axis for TB vaccine design. **S.A.K.**

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FROM THE EDITOR

"Virulent *Mycobacterium tuberculosis* infection induces the formation of follicular-like lymphoid structures within lung granulomas. Here, the authors find that B cells in these structures are needed to recruit T_{FH} cells, but the other functional activities of B cells (including antigen presentation) are dispensable. Instead, it is the T_{FH} cells' 'help' that is crucial for the formation of the granuloma structure and control of the *Mtb* bacilli." **Laurie Dempsey, Senior Editor, *Nature Immunology*.**