Lung lymphoid neogenesis in cystic fibrosis: a model of adaptive responses to bacteria?

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Frija-Masson and co-workers draw definite conclusions on the role of pathogens for lymphoid neogenesis in the CF lung http://ow.ly/v4iH309MbCs


Cystic fibrosis and non-cystic fibrosis bronchiectasis share as their main clinical hallmark repeated lung infections by opportunistic pathogens. In the normal adult lung, almost no lymphoid tissue is observed, in contrast to fetal and paediatric lungs [1] and in contrast to upper airways [2]. Neogenesis of bronchial-associated lymphoid tissue (BALT), also referred to as induced BALT (iBALT) or ectopic lymphoid follicles, has been observed in several chronic lung diseases, including chronic obstructive pulmonary disease (COPD) [3], lung cancer [4], pulmonary hypertension [5], post-transplant restrictive allograft syndrome [6] or rheumatoid lung [7], as well as possibly, to some extent, in asthma [8]. A distinction should thus be made between aggregates of B-cells without specific reorganisation and lymphoid follicle structures as observed in primary (bone marrow, thymus) and secondary lymphoid organs (lymph nodes, spleen and Peyer’s patches). Lymphoid follicles contain mature naïve and memory B-cells, T-cells, dendritic cells and follicular dendritic cells organising in germinal centres and vascularised with lymphatics and high endothelial veinules. Such lymphoid follicles in non-lymphoid organs are called mucosal-associated lymphoid tissue in mucosal tissues and tertiary lymphoid follicles in other organs.

Frija-Masson et al. [9] reveal, in this issue of the European Respiratory Journal, the presence of lymphoid follicles in peribronchial areas of the lungs from patients with cystic fibrosis or with localised bronchiectasis, following careful examination of their structures including B- and T-cells, germinal centres and high-endothelial veinules. In addition, by using an elegant murine model of instillation of microbeads coated with Staphylococcus aureus or Pseudomonas aeruginosa, they were able to recapitulate in these mice the formation of lung lymphoid follicles upon persistent infection. Furthermore, they highlighted in both situations (patients with bronchiectasis and infected mice) increases in IL-17 and the B-cell-attracting chemokine CXCL13 and, to some extent, CXCL12. Accordingly, another recent study reported the presence of lymphoid follicles in the lungs of patients with end-stage cystic fibrosis, localised in peribronchial as well as in parenchymal and perivascular areas [10].

The mechanisms of lymphoid neogenesis remain poorly understood, notably in the lung. It has been shown that the B-cell chemokine CXCL13 is upregulated in COPD and pulmonary hypertension, as well as in
smoking mice [5, 11], presumably produced by stromal fibroblasts and attracting (in areas with abundant reticular fibres and collagen IV) mature B-cells and a subset of follicular T-helper cells which express high levels of its receptor CXCR5. Importantly, CXCL13 is probably induced following lymphotoxin-β receptor activation and early upregulation of the IL-1α pathway, as recently shown following influenza infection of mice [12]. Other B-cell chemokines, such as CXCL12 and CCL19, 20 and 21, probably also contribute to attract circulating CCR6+ CXCR5+ B-cells to lung lymphoid follicles [5, 13], while factors such as B-cell activating factor further promote B-cell survival and immunoglobulin synthesis [14].

The role of lung lymphoid follicles remains debated [15–17], as they can probably be viewed as beneficial or detrimental according to the primum movens, and thereby to the context, of their genesis relating to immune protection against pathogens or autoimmunity against self-antigens. In the model of influenza infection, a protective role of iBALT and secreted antibodies can be demonstrated [18]. The role of bacteria as inducers of lymphoid follicles in the lung has first been reported by Delventhal et al. [19] following instillation of Haemophilus in the lungs of pigs. This was reproduced by Fleige et al. [20] upon repeated instillations of P. aeruginosa in mice, which induced BALT following IL-17-driven CXCL12, despite the absence of follicular dendritic cells, in contrast to BALT induced by the modified vaccinia virus Ankara. The results of the study reported by Freia-Masson et al. [9] rather suggest that the recruitment/differentiation of these dendritic cells, observed in lymphoid follicles induced by both P. aeruginosa and S. aureus, depends on the persistence of the bacterial trigger rather than the nature of the pathogen. The chronicity is thus a key issue, very relevant to cystic fibrosis lung disease, which is usually characterised even at early stages, by the chronic or repeated presence of opportunistic pathogens in the lung. These infection-induced lymphoid follicles are presumably beneficial, at least in part, by providing adaptive responses to bacteria (e.g. to P. aeruginosa) which can be seen in most adult cystic fibrosis patients [21, 22] and, in clinical practice, serum anti-P. aeruginosa antibodies may help to assess the chronicity of P. aeruginosa infection, along with Leed’s criteria [23]. In contrast, at the other end of the spectrum, autoantibody production associated with some phenotypes of chronic lung diseases could play a pathogenic role, as reported in pulmonary hypertension [24]. This dichotomic view of infection-versus autoimmunity-related neolymphogenesis is however challenged by recent observations in cystic fibrosis. Although bacterial infection was for long suspected to induce BALT in the cystic fibrosis lung, as nicely confirmed herein using appropriate tools [9], autoantibodies to bactericidal permeability-increasing protein (BPI) as well as to carbamylated proteins are frequently found in patients with cystic fibrosis (up to 80% of cases) and correlated with worse prognosis in...
terms of mortality, lung function, exacerbations and pan-resistant \textit{P. aeruginosa} \cite{25}. Interestingly, a recent study unravelled that \textit{P. aeruginosa}-mediated formation of neutrophil extracellular traps results in BPI cleavage by \textit{P. aeruginosa} elastase \cite{26}, suggesting a novel mechanism of autoimmunity and indicating that complex relationships link infection, (neutrophilic) inflammation and autoimmunity in the cystic fibrosis lung (figure 1).

The next question we need to answer to restore the delicate balance for mucosal tolerance and immunity in the lung, is how can we intervene in cystic fibrosis to transform lymphoid follicles into \textit{true friends} by switching off the production of autoantibodies and promoting the protective response by anti-bacterial antibodies? Besides sterile pathogenic mechanisms operating in cystic fibrosis \cite{27}, addressing these issues may pave the way for current and future studies of the complex interactions between bacteria and airway host tissues in the chronic diseased lung, which probably underlie disease severity, and for which \textit{FRIJA-MASSON et al.} \cite{9} have laid an important foundation stone.

References