



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>

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Cystic fibrosis and non-cystic fibrosis bronchiectasis share as their main clinical hallmark repeated lung infections by opportunist 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 venules. 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 venules. 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

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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-1 α 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 FRIJA-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 Leu'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

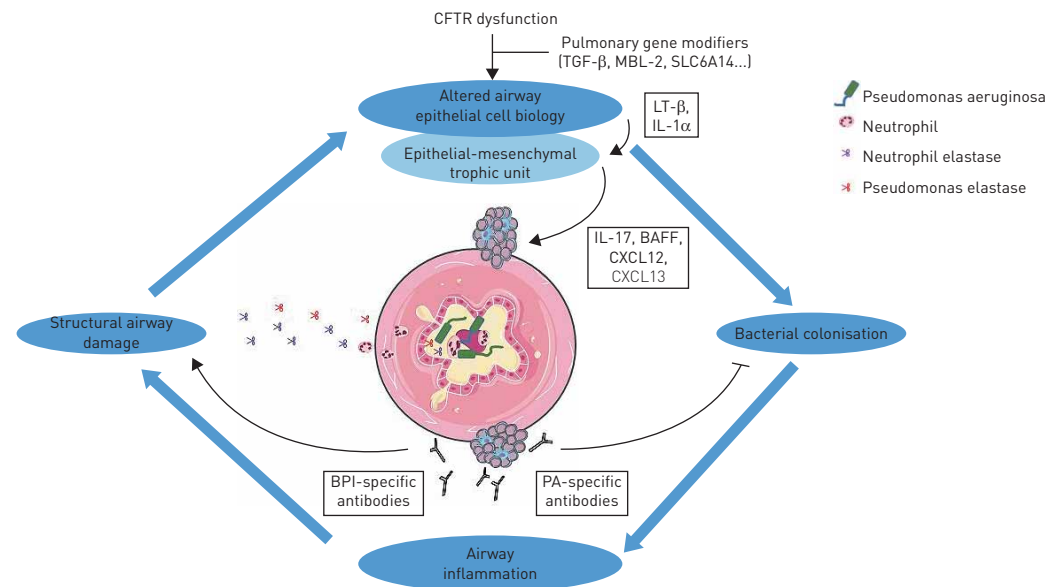


FIGURE 1 Schematic overview of peribronchial lymphoid follicles in the pathophysiology of cystic fibrosis. Upon activation by lymphotoxin (LT)- β and interleukin (IL)-1 α , airway epithelial and mesenchymal cells secrete chemokines that attract B-cells and contribute to local lymphoid neogenesis. Lymphoid follicles are probably the site of adaptive immunity for the production of anti-*Pseudomonas* (PA) antibodies as well as anti-bactericidal permeability-increasing protein (BPI) autoantibodies, which are presumably beneficial or detrimental, respectively. Images from Servier Medical Art were used to generate this figure. CFTR: cystic fibrosis transmembrane conductance regulator; TGF- β : transforming growth factor- β ; MBL-2: mannose-binding lectin 2; SLC6A14: sodium- and chloride-dependent neutral and basic amino acid transporter B(0+); BAFF: B-cell activating factor; CXCL: chemokine [C-X-C motif] ligand.

terms of mortality, lung function, exacerbations and pan-resistant *P. aeruginosa* [25]. Interestingly, a recent study unravelled that *P. aeruginosa*-mediated formation of neutrophil extracellular traps results in BPI cleavage by *P. aeruginosa* elastase [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 *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 [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 FRIJA-MASSON *et al.* [9] have laid an important foundation stone.

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