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EDITORIAL

To reg or not to reg: that is the question in COPD

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Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide, resulting in an economic and social burden that is in continuous progression [1]. In recent decades, significant improvements have been made to our understanding of COPD pathogenesis. In particular, it has been convincingly demonstrated that in patients with COPD, chronic inflammation is present not only in the lung but extends outside the organ, involving regional lymph nodes and systemic circulation [2–6]. Several cell lines, including macrophages, neutrophils and lymphocytes, participate in the inflammatory response that characterises COPD [7]. In particular, it has been proposed that CD8+ T-cells may be crucial in orchestrating the inflammatory response in this disease. Indeed, CD8+ T-lymphocytes infiltrate both central and peripheral airways [2, 3], lung parenchyma and pulmonary arteries [4]; not only are CD8 T-cells increased in all these compartments, they are also related to the degree of airflow limitation, suggesting that they may play an important role in the tissue damage and remodelling processes that determine the functional alterations in COPD.

Although nearly all smokers have some evidence of lung inflammation, only a minority of these will have an amplified response, and the mechanisms for this amplification are still poorly understood. It has been hypothesised that susceptibility to COPD may arise from a shift from the nonspecific innate response present in every smoker toward an adaptive immune response with features typical of autoimmune processes [8–10]. Indeed, in subjects with smoking-induced emphysema, the immune response has the characteristics of a type 1 response with production of interferon-γ [10], which is crucial in the activation of macrophages, not only in response to viral and bacterial pathogens but also to auto-antigens. CD8+ T-cells also express CXCR3, a chemokine receptor that is known to be preferentially expressed on type 1 cells, and this expression is paralleled by a strong epithelial upregulation of its ligand CXCL10 [11]. The interaction between CXCL10 and CXCR3 induces the release of matrix metalloproteinase (MMP)-12 [12] from macrophages and, similarly, type 1 inflammation determines upregulation of other metalloproteinases, such as MMP-2 and -9 [13–15]. As MMPs are potent enzymes that degrade elastin and collagen, these data suggest a possible mechanism through which T-helper cell type 1 lymphocytes can drive the progression of emphysema. All these diverse observations were elegantly unified in the recent paper by LEE *et al.* [10], demonstrating that the immune response in COPD has the features of an autoimmune process directed against elastin peptides.

In this issue of the *European Respiratory Journal* (*ERJ*), BARCELÓ *et al.* [16] add new details to our knowledge of the functional characteristics of T-lymphocytes in COPD. BARCELÓ *et al.* [16] analysed markers of activation (reduced CD28) and maturation (CD45RA/CD45R0) in lymphocytes isolated from bronchoalveolar lavage (BAL) and peripheral blood of smokers with COPD. By comparing the results to the appropriate groups of smoking and nonsmoking controls, they provide new insights into the mechanisms regulating the fate of lymphocytes in the lungs, in the context of either tobacco smoking or COPD. First, BARCELÓ *et al.* [16] found reduced CD28 expression (an index of activation) in BAL lymphocytes from all smokers, irrespective of the presence of COPD. This effect was not observed in peripheral blood T-lymphocytes, suggesting that a selective recruitment (or local activation) of T-lymphocytes may be a specific response to the lung injury induced by smoking. They also demonstrated an increased percentage of CD8+ T-lymphocytes expressing CD45RA (and a reduced expression of CD45R0) in patients with COPD as compared to smokers with normal lung function. As T-cell maturation involves sequential expression of CD45RA (naïve T-cells), CD45R0 (memory) and, again, CD45RA (effector/cytotoxic) [17, 18], these findings suggest that activated CD8+ T-cells only reach a state of final maturation in patients with COPD. These cells are highly cytotoxic, with a strong expression of intracytoplasmic perforin and granzyme, and therefore have a striking potential for determining tissue damage [19].

It is interesting to note that expansion of cells with these characteristics can also be found in other clinical conditions involving chronic activation of the immune system, such as viral infections, rheumatic and autoimmune diseases or tumours [19]. Finally, another important finding of the study by BARCELÓ *et al.* [16] was that a subset of T-regulatory cells (Treg; CD4+CD25+) was increased in smokers with normal lung function when compared to both never-smokers and smokers with COPD. Treg are a small subpopulation of lymphocytes that have been identified as key immunomodulators, which preserve the homeostasis of the immune system avoiding unnecessary reactions. Many different Treg subsets have been described, such as CD8+ Treg cells, natural killer cells and several different CD4+ Treg cell subsets, which include naturally occurring Treg cells (CD4+CD25+) and adaptive Treg cells [20].

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The picture that emerges from these data is that, in all smokers, there is a certain degree of activation of T-lymphocytes; however, in those smokers who maintain normal lung function, despite considerable smoking consumption, this activation is restrained by the upregulation of Tregs. By contrast, in smokers who develop COPD and who are incapable of having an effective Treg response, the immune reaction progresses uncontrolled, involving the final differentiation of T-cells into the cytotoxic phenotype. These events will ultimately lead to the progressive lung tissue destruction that characterises emphysema. A lesson that can be learnt from this study is that although much of the ongoing research is focused on determining mechanisms of susceptibility to COPD, it is equally important to understand the mechanisms of resistance to COPD, which are activated in heavy smokers with normal lung function. By knowing the way in which these individuals manage to preserve their lung integrity, despite the unavoidable harm of cigarette smoke, we can learn a lot about the mechanisms of immune tolerance that are broken in COPD.

The study by BARCELÓ *et al.* [16] makes an important contribution; however, it is not without limitations. First, the authors did not fully characterise CD8+CD45RA+ cells to conclusively demonstrate that they represent the final stage of maturation. This would include characterisation of other functional markers, an aim that seems worth pursuing in future studies. In addition, they did not fully analyse the functional characteristics of Treg cells; for example, by examining the expression of transforming growth factor-β besides that of interleukin-10. Finally, they analysed lymphocytes from BAL; it is presently unknown whether this would reflect the functional characteristics of T-lymphocytes isolated from the lung tissue.

The data presented by BARCELÓ *et al.* [16] in this issue of the *ERJ* add new information to the debate on the role of lung inflammation in COPD. On the one hand, there is evidence that amplification of the inflammatory response is invariably associated with the establishment of airflow limitation in smokers [2–6], that this response progressively increases as the disease worsens [21, 22] and that it is required for the development of emphysema in some experimental models [23]. This seems to indicate that, instead of driving an effective immune response, T-lymphocytes are more likely to have detrimental effects, as suggested by BARCELÓ *et al.* [16]. On the other hand, it is equally plausible that T-lymphocytes may maintain their protective role in COPD, by driving an effective immune response which is essential to overcome infectious agents.

In conclusion, despite the increasing body of research on inflammatory mechanisms in chronic obstructive pulmonary disease, it is still uncertain whether the immune response is friend or foe to the patient. This takes us back to the concept that all our work, our efforts and our newly gained insights illuminate what is both our best friend and our worst foe: doubt. That, by opening the road to new paths, makes us move on.

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