Which CD8$^+$ T-cells in asthma? Attacking or defending?

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CD8$^+$ cells are associated with lung function decline in asthma but the subtype of CD8$^+$ cells has to be better defined http://ow.ly/iPQz300NuOT

There is considerable need to understand, and interest in understanding, the factors influencing the long-term prognosis of patients with asthma, especially considering the increase in life expectancy of this population. Thus, predicting the trajectories of lung function decline in ageing asthmatics has become an important task for current and future asthma management.

Even though there have been multiple studies with longitudinal assessment of lung function in asthma [1, 2], to date, the relationship between the underlying airway pathology and the rate of functional decline has been poorly addressed in prospective studies. Den Otter *et al.* [3], in the present issue of the *European Respiratory Journal*, have addressed this topic in a cohort of patients with mild-to-moderate asthma who were followed for 14 years, and underwent bronchoscopy at the beginning of the study and at the end of follow-up. The numbers of CD8$^+$ and CD4$^+$ cells in bronchial biopsies at baseline correlated with the subsequent decline in lung function. The subjects with the highest function decline had higher counts of CD3$^+$ and CD8$^+$ T-cells and presence of granzyme B in biopsies taken at follow-up. Let's consider two aspects of this study.

First: the functional decline

The average lung function decline in this population of mild-to-moderate asthmatics was small (21 and 31 mL per year for pre- and post-bronchodilator forced expiratory volume in 1 s (FEV_1), respectively) and within the normal limits for a population of this age, a finding that is in agreement with data from population-based and clinical longitudinal studies [2, 4, 5]. Interestingly, the pioneering longitudinal study by Lange *et al.* [1] reported a greater rate of lung function decline in asthmatic patients, possibly because their asthmatic population included current smokers and subjects with fixed airflow limitation.

As a general message, the course of FEV_1 decline in cohorts with a typical pattern of asthma is generally favourable and largely comparable to that of the normal population. Unfortunately, this mild rate of decline is not the norm in all asthmatics since, as we have previously shown [6], asthmatic subjects who had developed chronic airflow limitation had accelerated lung function decline, about 50 mL per year, comparable to that of chronic obstructive pulmonary disease (COPD) patients. By contrast, asthmatic patients in whom airflow obstruction is still fully reversible had a much slower decline (18 mL per year), similar to that of the study den Otter *et al.* [3]. Recent epidemiological data add new, important information on the trajectories of chronic airflow limitation in asthma. In adults with asthma and fixed airflow limitation, which is now often labelled as asthma–COPD overlap syndrome, lung function decline is affected by the age of recognition of asthma, being steeper in those with late asthma onset and much slower in those with an early onset of the disease [4, 5]. This information complements the emerging picture in childhood asthma, which shows that most children with persistent asthma have a reduced growth of lung function and are at increased risk for fixed airflow obstruction in early adulthood [7, 8]. Thus, the presence

Received: May 24 2016 | Accepted: May 26 2016

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

of chronic airflow obstruction in asthma may be the result of either a reduced lung function growth in early childhood or a steeper decline in adulthood.

A very telling observation about the results of the study den Otter *et al.* [3], which defines the nature of the disease, is that the FEV_1 decline in the first 7.5 years period of follow-up did not correlate with that in the second period of follow-up, suggesting that the fall in lung function could be largely episodic. This is a crucial point to take into account when examining the clinical implications of this and other studies. Much of the current debate on lung function decline in asthma has considered it as a continuum, despite the disease being by its nature episodic. Of importance, although the trajectories of lung function may differ significantly among subjects with asthma, the only factor that seems consistently associated with lung function decline is the number of acute exacerbations [9, 10]. Thus, it could be questioned whether the average lung function decline *per se*, without considering the acute worsening of symptoms, is the right outcome to capture the impact of a disease that is characterised by repeated acute events.

Second: the possible role of $CD8^+$ T-cells in asthma

The main finding of the study den Otter *et al.* [3] was that the decline of FEV_1, even if mild, correlated with the number of $CD4^+$ T-cells at baseline but more consistently, both at baseline and follow-up, with the number of $CD8^+$ T-cells in airway biopsies. Asthma has been traditionally associated with an expansion of $CD4^+$ type 2 helper T (Th)-cells in response to allergen exposure and these cells are considered mainly responsible for the disease. Thus, it is not surprising that a correlation between $CD4^+$ T-cells and disease progression is found. However, what might appear somewhat surprising is the presence in the asthmatic airways of $CD8^+$ T-cells, which are usually thought to be cytotoxic T (Tc)-cells. An interesting question would be, what is the role of the $CD8^+$ cells populating the asthmatic airways? But even a more interesting one would be, which kind of $CD8^+$ cells is involved? There is increasing evidence that the $CD8^+$ T-cell can develop, as the $CD4^+$ cells do, a subset diversification according to need and the milieu in which the cell operates. As such, $CD8^+$ T-cells can diversify not only into Tc1-cells producing interferon (IFN)-γ, and Tc2 cells producing interleukin (IL)-4, IL-5 and IL-13, but also into $CD8^+$ regulatory T-cells, Tc9-cells and Tc17-cells, all of which have different functions [11–16]. But which subset, or subsets are found in asthma?

Could these $CD8^+$ cells be Tc1-cells?

This is very likely. The presence of granzyme B in this and other reports [17] testifies to their cytotoxic function being able to produce lung damage. $CD8^+$ Tc-cells play a major role in the defense against viral infections and it is well known that rhinovirus is particularly important in asthma. There is clinical evidence that asthmatic patients, once infected with viruses, have more severe clinical manifestations than normal subjects [18], probably because respiratory viruses can persist in the airways long after the acute episode. Possibly, the $CD8^+$ T-cells in the airways represent effector–memory $CD8^+$ Tc1-cells that have remained in the airway after previous viral infections, waiting to defend against the next virus attack [11]. The unfavourable outcome in asthmatic patients of a usually mild event, *i.e.* rhinovirus infection, has been linked to impaired epithelial immune responses, with deficient IFN production, present in asthmatics from the very early stage of the disease [19]. This impaired immune response is strictly associated with the immunopathological milieu in the airways, mainly with the degree of epithelial damage and IL-4 production. Thus, it could be speculated that the presence of IFN-γ-producing $CD8^+$ Tc-cells might be useful to support an antiviral response that is known to be impaired in asthmatic airways.

Could these $CD8^+$ cells be Tc2-cells instead?

Yes, they could. There is evidence that, similarly to $CD4^+$ T-cells, $CD8^+$ T-cells can also differentiate into type 2 cytokine-producing cells [12]. In particular, some $CD8^+$ T-cells can be induced by IL-4-producing $CD4^+$ cells to differentiate into $CD8^+$ IL-13-producing Tc2-cells [13], but their role in the pathogenesis of asthma may be under recognised. A factor that might facilitate the induction of $CD8^+$ Tc2-cells by IL-4 is the expression of the high-affinity receptor for leukotriene B4 (BLT1) by the $CD8^+$ T-cells. In fact, it has been shown that the subset of $CD8^+$ T-cells expressing BLT1 and producing IL-13, but not the total number of $CD8^+$ T-cells, was correlated with the degree of airflow obstruction in asthmatic subjects [12]. These cells have a potentially important role in dictating the severity of asthma, since IL-13 is a critical mediator of airway hyperresponsiveness and mucus hyperproduction, and $CD8^+$ Tc2-cells seem to be fairly resistant to corticosteroids treatment. There might be some positive news about these IL-13-producing $CD8^+$ T-cells, since it was recently shown that vitamin D can downregulate the conversion of $CD8^+$ T-cells into IL-13-producing Tc2-cells mediated by IL-4, thus being beneficial to asthmatic subjects [14]. Further studies targeting this subset of $CD8^+$ T-cells would be necessary to establish their causative role in asthma.

DOI: 10.1183/13993003.01037-2016

Another possibility: could these CD8$^+$ cells be Tc9-cells?

The CD8$^+$ Tc9-cells, which produce IL-9, are newcomers in the mechanism of asthma. These cells, which display a diminished cytotoxic activity, are induced in the presence of IL-4 and transforming growth factor-β, and can act as strong "helpers" for the activity of CD4$^+$ Th-cells. In particular, it has been shown that CD8$^+$ Tc9-cells cannot induce the key features of asthma, revealing that they are not pathogenic by themselves; however, they can play a supportive role for the initiation of CD4$^+$ Th2-mediated airway inflammation at a stage when Th2-cells are not sufficient to induce the disease by themselves [15].

Could these CD8$^+$ cells be regulatory T-cells?

In other words, could they be defending instead of attacking? The importance of the CD4$^+$ Foxp3$^+$ regulatory T-cells and their constitutively expressed CD39 in the regulation of the immune response is well known. Less known is that even CD8$^+$ cells can switch to a regulatory phenotype when exposed to certain cytokines. Indeed, in the presence of IL-4 and IL-12, CD8$^+$ T-cells can become regulatory, and exert their suppressive activity by contact-dependent mechanisms and by the production of IL-10. While these CD8$^+$ T-cells lack Foxp3, their regulatory properties depend on the expression of CD39, as is the case for CD4$^+$ Foxp3$^+$ cells. Interestingly, it has been shown that CD8$^+$ T-cells can develop this Foxp3-independent suppressive activity only in the absence of alarmins [16]. Thus, this mode of action would promote peripheral tolerance to immunogenic antigens that do not cause tissue damage.

Summary

It is fairly clear that when we speak about the role of CD8$^+$ T-cells in asthma, we have to be much more precise. Which of CD8$^+$ T-cells described here is at fault? A combination of them? Possibly. Since respiratory viruses and allergens are common triggers in asthma, both virus-specific and antigen-specific CD8$^+$ T-cells would be expected to contribute to the worsening and decline of lung function in asthmatic subjects [12]. However, CD8$^+$ T-cells could also act as defending cells, thus attenuating the severity of asthma, and the mildness of the disease in the asthmatic subjects described by DEN OTTER *et al.* [3] would support this possibility. Whether the CD8$^+$ T-cells play a protective or a pathogenic role is probably determined by the conditions in the local environment. For example, the presence of IL-4 produced by CD4$^+$ T-cells is an important determinant for the shift of CD8$^+$ T-cells to most of the different CD8$^+$ subpopulations described. Therefore, we should not forget that the CD4$^+$ T-cell, which is also correlated with the functional decline in the study by DEN OTTER *et al.* [3], remains the protagonist in orchestrating the inflammatory response in asthma.

In conclusion, it would be very helpful to better understand which CD8$^+$ cells might be playing a role in asthma before we start a campaign against this cell, always remembering that some of these CD8$^+$ cells are effector–memory Tc-cells, keeping an eye open to possible viral infections in these very susceptible patients.

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DOI: 10.1183/13993003.01037-2016