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Commentary

Chronic Obstructive Pulmonary Disease, Neutrophils and Bacterial Infection: A Complex Web Involving IL-17 and IL-22 Unravels

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Neutrophils provide innate immune defence against microbes such as bacteria. Neutrophilic airway inflammation is a characteristic feature of chronic obstructive pulmonary disease (COPD) (Hogg et al., 2004), a condition that is commonly caused by cigarette smoking. Neutrophils activated by the inhalation of toxic particles contribute to the pathophysiology of COPD by secreting proteases that cause tissue destruction and by releasing mediators that promote airway inflammation. On the one hand, it could be therapeutically beneficial to reduce neutrophil activity in COPD lungs. On the other hand, one has to be careful about preserving anti-bacterial defence. This is particularly relevant for the subset of COPD patients who have persistent bacterial colonisation and/or acute bacterial exacerbations, often caused by nontypeable *Haemophilus influenzae* (NTHi) or *Streptococcus pneumoniae* (Desai et al., 2014).

The chemokine receptor CXCR2 plays a key role in neutrophil chemotaxis. The CXCR2 antagonist MK-7123 administered for 6 months reduced sputum neutrophil numbers and improved lung function in COPD patients (Rennard et al., 2015), supporting the concept that reducing neutrophilic airway inflammation is beneficial for COPD patients. However, this orally administered drug excessively reduced blood neutrophil counts in some patients. Furthermore, there were more infections in the optional 12 month extension period in patients treated with MK-7123 compared to placebo. This highlights the balance required with anti-neutrophil therapies in COPD; potential clinical benefit weighed against risk of infection.

Th17 cytokines, including IL-17 and IL-22, fight bacteria by various mechanisms, including the upregulation of anti-microbial proteins and the secretion of neutrophil chemokines, such as CXCL8, by airway epithelial cells (McAleer and Kolls, 2014). Th17 cytokines are produced by various cell types, including conventional lymphocytes and type 3 innate lymphoid cells, in response to the secretion of IL-1β, IL-23 and IL-6 by antigen presenting cells (APCs). IL-17A is the most well studied Th17 cytokine in COPD; the expression of this cytokine is increased in the lungs of stable COPD patients compared to controls (Eustace et al., 2011; Di Stefano et al., 2009). Roos et al. showed that IL-17A levels were increased during acute exacerbations of COPD, but only when NTHi was present (Roos et al., 2015). Roos et al. also demonstrated that cigarette smoke (CS) exposed mice (for 4 days or 8 weeks) had greater IL-17A levels and lung neutrophilia after exposure to NTHi compared to room air (RA) exposed mice. This excessive neutrophilic response was absent when an anti-IL17A neutralising antibody was administered, and when IL-17A knockout mice were used. Interestingly, these knockout mice did not have a defect in NTHi bacterial clearance. The authors suggest that targeting IL-17A may be beneficial during COPD exacerbations, because of the potential to reduce neutrophilic inflammation while having no detrimental effect on bacterial clearance.

In *EBioMedicine*, Pichavant et al. used 12 week CS exposure to generate mice with COPD-like lung disease (Pichavant et al., 2015). There was increased neutrophilic inflammation and bacterial load after *S. pneumoniae* exposure in CS compared to room air (RA) exposed mice. Furthermore, there were lower IL-17 and IL-22 levels in infected CS-exposed mice, and lower levels of the Th17 inducers IL-1β and IL-23 produced by APCs. The suppressive effect of CS on various cytokines has also been observed in previous human studies using COPD lung cells, such as macrophages (Metcalfe et al., 2014). IL-22 administration before bacterial challenge increased bacterial clearance in CS exposed mice. There was no change in lung neutrophil numbers, but there were increased levels of anti-microbial peptides and IL-17 production, and less histological evidence of *S. pneumoniae* associated lung damage. IL-17 was not administered to combat bacterial infection, as this cytokine may contribute to COPD pathophysiology (Eustace et al., 2011; Di Stefano et al., 2009; Roos et al., 2015). These results strongly suggest a role for IL-22 in promoting anti-bacterial immunity in the context of chronic cigarette smoke exposure. Experiments using peripheral blood mononuclear cells showed defective IL-17 and IL-22 secretion from COPD compared to control cells after exposure to *S. pneumoniae*, providing validation of mouse model results by using relevant cells from patients with disease.

These studies by Roos et al. (Roos et al., 2015) and Pichavant et al. (Pichavant et al., 2015) provide potentially important insights into the complex interactions between Th17 cytokines, neutrophilia and bacterial exposure in COPD. In CS-exposed mice, NTHi and *S. pneumoniae* infection both caused enhanced lung neutrophilia, but IL-17 production was enhanced with the former and decreased with the latter. There may be differences between the experimental details of the mouse CS exposure protocols, such as duration of CS exposure, that could alter

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the responses to bacteria. However, in both CS models the neutrophilic response was increased by bacterial exposure, but the IL-17 response was bacterial species dependent. Furthermore, both papers convincingly back up mouse data with results from COPD patients. Where does this leave us with the potential for targeting IL-17, given its potential pro-inflammatory role in COPD? It seems that suppressing IL-17 may be a useful anti-inflammatory approach in the context of NTHi infection, but not during *S. pneumoniae* infection.

Would pharmacological modulation of IL-22 be beneficial in COPD patients? There appears to be a defect in the IL-22 response to *S. pneumoniae* in COPD patients, and animal model data suggests that modulating IL-22 levels improves bacterial clearance and inflammation in a manner that does not involve any change in neutrophil numbers (Pichavant et al., 2015). It would be important to know if this defect in IL-22 production is also present after exposure to NTHi in COPD patients and animal models.

We are becoming increasingly aware of the heterogeneous nature of COPD, with specific treatments being required for subsets of patients with distinct characteristics (Woodruff et al., 2015). The endotype concept, a group of patients defined by a biological mechanism, allows pharmacological targeting of mechanisms rather than clinical characteristics (Woodruff et al., 2015). Targeting the defective IL-22 response to *S. pneumoniae* would be an example of endotype-driven treatment. Targeting the excessive IL-17 response to NHTi would be another example. The therapeutic index (benefit versus risk) of such approaches will be enhanced by definition of the patients most likely to benefit. As we move into the era of personalised medicine, one size will not fit all in COPD.

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