Macrophages, corticosteroids and COPD: what do we know?

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The numbers of pulmonary macrophages are increased in COPD. There is evidence that the function of these cells is altered in COPD, and that they contribute to the pathogenesis of the disease. Here we discuss our recently published pooled analysis of five previous macrophage publications. This confirmed that there is no difference in the corticosteroid sensitivity of COPD macrophages compared to controls. We discuss the limitations of corticosteroids for the suppression of macrophage derived CXCL8, which is a neutrophil chemoattractant. We also discuss recent evidence for myeloid derived cell sub-populations in human lungs, and the relevance to COPD.

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Chronic obstructive pulmonary disease (COPD) is associated with an abnormal immune response to inhaled noxious particles, the most common of which is tobacco smoke [1]. The characteristic features of COPD are airflow limitation, parenchymal destruction and lung inflammation. Macrophage numbers are increased in the lungs of COPD patients [2]. These cells may have a pro-inflammatory role in COPD, through the secretion of cytokines and proteases that contribute to inflammation and tissue destruction. On the other hand, there is a gene expression pattern in COPD macrophages more suggestive of an anti-inflammatory phenotype caused by cigarette smoking [3]. Historically, macrophages have been categorised as classically activated M1 cells with pro-inflammatory activity or alternatively activated M2 cells with anti-inflammatory and tissue repair functions [4]. This classification appears to be an oversimplification, as an increasing complexity of macrophage subtypes are identified based on cell surface markers [4], and it appears that COPD lung macrophages are not simply pro-inflammatory cells.

Pulmonary macrophages reside in the interstitium, airways, and alveolar spaces of the lungs (figure 1), and their role is dependent on the microenvironment [5]. Alveolar macrophages patrol the airways, and are adept at removing airborne particles and microbes without disturbing the homeostatic balance. However, chronic exposure to cigarette smoke alters the characteristics of alveolar macrophages [3]. COPD alveolar macrophages have a reduced ability to phagocytose bacteria, and to efferocytose particles [6, 7]. Furthermore, there is some evidence that COPD alveolar macrophages have a reduced ability to secrete pro-inflammatory cytokines in vitro [8, 9], although we found similar cytokine levels in COPD patients and controls in a
recent pooled analysis of our lung macrophage studies \[^{[10]}\]. This variation between studies may be explained by lower cytokine responses to bacteria and toll like receptor agonists in COPD patients with exacerbations compared to COPD patients without exacerbations \[^{[11]}\]. Some COPD patients are prone to bacterial colonisation associated with exacerbations; reduced innate immune function, both in terms of bacterial clearance and the production of pro-inflammatory cytokines, is likely to contribute to the persistence of bacteria in these individuals.

Inhaled corticosteroids (ICS) are drugs commonly used to reduce inflammation in COPD patients. Corticosteroids bind to and activate the glucocorticoid receptor (GR), resulting in GR nuclear translocation and the subsequent transrepression of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby inhibiting pro-inflammatory gene transcription \[^{[12]}\]. ICS have a limited impact on exacerbations, reducing the rate of exacerbations by approximately 25% \[^{[13, 14]}\]. This effect is greater in those with higher blood eosinophil numbers \[^{[15, 16]}\]. There is a need to understand why ICS have limited effects in a large number of COPD patients.

It has been reported that corticosteroids are less effective at reducing cytokine production from COPD lung macrophages compared to controls \[^{[17]}\]. We have failed to reproduce this in five previous studies \[^{[18-22]}\]. We have recently published a pooled analysis of these data, to increase statistical power \[^{[10]}\]. The combined dataset confirmed that the inhibitory effect of corticosteroids on lipopolysaccharide (LPS) induced cytokine production from COPD lung macrophages is similar to controls. Interestingly, corticosteroid effects varied between cytokines. The maximal inhibition of chemokine C-X-C motif ligand 8 (CXCL8) was below 60%, while for other cytokines such as tumour necrosis factor-α (TNF-α) this was approximately 80%. This is an important observation, as the levels of CXCL8 are increased in the lungs of COPD patients \[^{[23]}\] and CXCL8 is an important neutrophil chemoattractant \[^{[24]}\]. Neutrophilic airway inflammation is likely to continue if CXCL8 secretion is only partially suppressed by corticosteroids.

A recent study by Cosio et al. demonstrated that non-typeable Haemophilus influenzae induced interleukin-1β (IL-1β), IL-6, and CXCL8 production were completely corticosteroid insensitive (no inhibition observed) in both COPD and control lung macrophages, while 56% inhibition was observed for TNF-α \[^{[25]}\]. Using a different stimulus (live bacteria instead of LPS), these results confirm our pooled analysis showing similar corticosteroid sensitivity in COPD and control macrophages, and that corticosteroid sensitivity varies between cytokines. The complete lack of effect on some cytokines, including CXCL8, is likely to be very relevant to the failure of corticosteroids to prevent bacterial associated neutrophilic inflammation in COPD.

Previously we have shown that supernatants from COPD lung macrophages induce neutrophil chemotaxis that is CXCL8 dependent, and that corticosteroids have little effect on this macrophage induced neutrophil chemotaxis \[^{[26]}\]. Furthermore, we have demonstrated that pulmonary neutrophils express very low levels of GR in both COPD patients and controls \[^{[27]}\]. We suggest a corticosteroid insensitive pathway in COPD involving a pulmonary macrophage-CXCL8-neutrophil axis (figure 2). We have studied using p38 mitogen activated protein kinase (MAPK) inhibitors with corticosteroids, and shown that a combination of a p38 MAPK inhibitor with corticosteroids causes maximal CXCL8 inhibition of up to 80%, whereas
Corticosteroids alone cause up to 60% inhibition \[18\]. P38 MAPK inhibitors as monotherapy have anti-inflammatory effects on macrophages, and also show a synergistic interaction with corticosteroids for a range of cytokines, thus enhancing the anti-inflammatory effects observed.

The proportion of pulmonary macrophage sub-populations is likely to determine individual corticosteroid responses. Pulmonary macrophages of differing densities respond differently to corticosteroids \[28\]. Recent studies have shown distinct sub-populations of myeloid derived cells in the lungs including alveolar macrophages and monocyte like cells \[29-32\]. These subpopulations can be identified using the cell surface markers cluster of differentiation 206 (CD206), CD14 and CD16 to identify cells with monocyte / macrophage characteristics, and CD1a and CD1c to identify pulmonary dendritic cells \[31, 32\]. Interestingly, there are monocyte derived subpopulations expressing dendritic markers. We do not yet know how these subpopulations are altered in COPD, and whether the effects of corticosteroids differ between subpopulations.

Unravelling the complexity of pulmonary macrophage subpopulations will be crucial to the development of new treatments targeted at COPD macrophages. Crucially, we need to know the characteristics of COPD macrophage sub-populations, and whether their function is altered in those patients who frequently exacerbate.

**Conflicting interests**

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Abbreviations

CXCL8: chemokine C-X-C motif ligand 8; COPD: chronic obstructive pulmonary disease; CD1α: cluster of differentiation 1a; CD1c: cluster of differentiation 1c; CD14: cluster of differentiation 14; CD16: cluster of differentiation 16; CD206: cluster of differentiation 206; GR: glucocorticoid receptor; ICS: inhaled corticosteroids; IL-1β: interleukin-1β; IL-6: interleukin-6; LPS: lipopolysaccharide; MMP-9: matrix metalloproteinase-9; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; p38 MAPK: p38 mitogen activated protein kinase; TNF-α: tumour necrosis factor-α.

References


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