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Mini-Review

Infiltrated Cells and Inflammatory Process in COPD

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Abstract

COPD is a complex inflammatory disorder that leads to the destruction of lung tissue and compromises the pulmonary function. The process involves innate and adaptive immunity, and is regulated by inflammatory cells infiltrated, which through the production of cytokines and chemokines perpetuate and exacerbate the inflammation.

Introduction

Chronic obstructive pulmonary disease (COPD) -localized in peripheral airways and lung parenchyma [1] and characterized by sustained inflammation of the airways [2]-, comprises chronic bronchitis, destruction of small airways, and disorganization of alveoli leading to destruction of lung tissue and declining pulmonary function. Although there are clearly two different clinical phenotypes of COPD -patients with small airway disease and those with emphysema-, neither links to underlying the mechanisms of disease have been found or the different populations have been identified [3].

Response to inflammation in COPD includes innate immunity -eosinophils, neutrophils, macrophages, mast cells, natural killer cells, unconventional T-cells defined by expression of heterodimeric T-cell receptors (TCRs) composed of γ and δ chains (γδ-T-cells), and dendritic cells (DCs)-, and adaptive immunity

-lymphocytes T and B- with a marked increase in inflammatory cells such as neutrophils, macrophages, T-lymphocytes and B-lymphocytes [4,5] linked through the activation of DCs [6].

Epithelial cells, endothelial cells and fibroblasts in the lung are also involved in the inflammatory process releasing inflammatory mediators. Inflammatory mechanisms are further upregulated during exacerbations [7]. Besides cells and mediators involved in the innate and adaptive immunity, reactive oxygen species (ROS), and the local imbalance of proteolysis and anti-proteolysis also contribute to damage the lung [8]. In addition, senescence affects lung structural and inflammatory cells and fibroblasts, with an unsatisfactory rate of repair and regeneration [9,10].

Inflammatory Infiltrated Cells

Neutrophils -considered the initiating cells in COPD- appear first at the sites of inflammation in response to chemoattractant interleukin (IL)-8 produced by damaged epithelium and endothelium [11,12], and produce mediators to further perpetuate inflammation.

Macrophages in COPD –predominantly "M1-like" proinflammatory macrophages [13], but also "M2-like" macrophages that may contribute to defective remodelling [14]- are regarded as key players in orchestrating the inflammatory response [15], and the number of macrophages present in the airways is associated with COPD severity [16].

Activated macrophages -through nuclear factor (NF)-kappaB activation, particularly during exacerbations [17-19]- release inflammatory mediators -IL-1β, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), monocyte chemotactic peptide (MCP)-1, CXC chemokines (such as CXCL1, CXCL8, CCL2), leukotriene B_4 (LTB_4) [20-22], reactive oxygen species (ROS) [23]-, and elastolytic enzymes including matrix metalloproteinase (MMPs) -MMP-2, MMP-9, MMP-12 [24]- and cathepsins K, L and S [25,26].

Macrophages from COPD patients show reduced phagocytic uptake of bacteria -*Haemophilus influenzae* or *Streptococcus pneumoniae* [27]- leading to chronic colonization of the lower airways, which may predispose to increased acute exacerbations [28], and reduced efferocytosis, which may contribute to the failure to resolve inflammation in COPD [29].

T-lymphocytes -cytotoxic ($CD8^+$) cells that kill infected or damaged cells, and T-helper ($CD4^+$) cells that release cytokines and coordinate the inflammatory response [5,30]- increase in lung parenchyma and airways of COPD patients and mediate the host defense in an interrelated way that may be important for the progression of inflammation in COPD [31,32].

T-helper cells ($CD4^+$) -specifically Th1 cytokine types with activated transcription factor STAT-4 in smokers with COPD [33] that are regarded as responsible for lung emphysema-, help perpetuating autoimmune responses through interferon gamma (IFNγ), which induces excessive proinflammatory responses that can lead to damage the lung. Meanwhile, $CD8^+$ T-cells induce apoptosis through release of perforins, granzyme-B and TNF-α [34]. $CD8^+$ cells and alveolar cell apoptosis are associated in emphysema.

Additionally, Th17 cells -regulated by IL-6 and IL-23 released from alveolar macrophages- may play a role in neutrophilic inflammation through IL-17A and IL-22 [35-37].

Inflammatory Mediators

Multiple cytokines orchestrate chronic inflammation in COPD [38]. Proinflammatory cytokines -such as TNF-α and IL-1β- amplify the inflammatory response and play a role in severe COPD, while Th2 cytokines -IL-4, IL-5, IL-9, IL-13- mediate allergic inflammation also involved in the disease, since inhibition of IL-5 and IL-13 have clinical benefits in selected patients [39].

TNF-α -highly expressed in stable COPD and further increased during exacerbations [40]- is a potent activator of NF-κB, which may in turn amplify the inflammatory response. However, the failure in clinical improvement of COPD with anti-TNF therapies -with serious adverse effects [41]- may be due to the fact that other proinflammatory cytokines -maybe IL-6, which has pleiotropic effects and amplifies inflammation- are driving the inflammatory process.

In COPD, chemokines play a significant role in attracting inflammatory cells into the lungs through G-protein coupled receptors. Thus, CXCL8 secreted from macrophages, T-cells, epithelial cells and neutrophils is chemotactic for neutrophils via CXCR2 [42], while CXCR3 ligands increase monocytes and lymphocytes chemotaxis in COPD patients [43], and CCL5 is also expressed in airways of COPD patients during exacerbations. Activates CCR5 on T-cells and CCR3 on eosinophils may be responsible for the increase of T-cells and eosinophils in the wall of large airways during chronic bronchitis exacerbations [44].

Conclusion

Both innate and adaptive immunity are activated in COPD in response to inflammation. A marked increase in inflammatory cells, mainly neutrophils, macrophages, T-lymphocytes and B-lymphocytes, drive the immune response and are responsible for the inflammation in the lung tissue. Other lung cells -epithelial, endothelial and fibroblasts- also play a role in the inflammatory process in COPD releasing inflammatory mediators. ROS and proteolysis imbalance -together with unsatisfactory repair due to senescence- contribute to the process, further upregulated during exacerbations.

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