

Inflammatory Cells, Angiogenesis, and Lymphangiogenesis

Subjects: [Allergy](#)

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The inflammation seen in the lungs of COPD patients involves both innate (macrophages, neutrophils, mast cells, eosinophils, basophils, natural killer cells (NK cells), $\gamma\delta$ T cells, ILCs, and dendritic cells (DCs)) and adaptive immunity (B and T lymphocytes). There is also evidence that structural cells, including BECs and alveolar epithelial cells, ECs, fibroblasts, and myofibroblasts, can contribute to inflammatory mechanisms and angiogenesis in COPD.

angiogenesis

angiopoietin

COPD

lymphangiogenesis

macrophage

1. Macrophages

Macrophages are the predominant immune cells in the human lung parenchyma and are the first line of defense against pollutants and microbial pathogens ^{[1][2]}. These cells play a fundamental role in orchestrating chronic inflammation in COPD. Macrophage density is markedly increased (up to 10-fold) in the airways, lung parenchyma, bronchoalveolar lavage (BAL) fluid, and sputum of COPD patients. Macrophages can be activated by CSE to release inflammatory mediators, including cytokines (e.g., TNF- α), chemotactic factors [CXCL1, CXCL8, CCL2, LTB₄], and reactive oxygen species (ROS). Alveolar macrophages also secrete elastolytic enzymes, including matrix metalloproteinases (MMPs) -2, -9, and -12, cathepsins, and elastase ^[3]. MMP-9 is the predominant elastolytic enzyme secreted by alveolar macrophages from patients with COPD.

Compelling evidence indicates that human macrophages are highly heterogeneous ^{[4][5][6][7][8]}. In the human lung, several subsets of macrophages have been identified ^{[5][6][7][9]}, and it has been suggested that M1-like macrophages predominate in COPD patients ^[10]. However, further studies using single-cell RNA sequencing are needed to characterize the macrophage subpopulations in COPD patients. Recent evidence indicates that rhinovirus impairs the innate immune response to different bacteria in alveolar macrophages from patients with COPD ^[11]. Human rhinovirus also induced the release of cytokines (e.g., IL-6, TNF- α , IL-10, CXCL8) from macrophages.

Primary human macrophages (HLMs) purified from human lung parenchyma express angiogenic (VEGF-A and -B) and lymphangiogenic factors (VEGF-C and -D) ^{[2][12]}. Secretory phospholipase A₂ (sPLA₂), an enzyme expressed in the airways of patients with lung diseases including COPD ^[13], enhances the expression and release of VEGF-A and -C from HLMs. HLMs activated by lipopolysaccharide (LPS) release VEGF-A, ANGPT1, ANGPT2, and VEGF-C ^[2].

2. Mast Cells

Mast cells are prominent immune cells in human lung parenchyma [7][14][15] and play a pivotal role in coordinating lung inflammation [16]. Mast cell density is increased in bronchial biopsies from COPD patients compared to healthy controls [17]. Activated rodent mast cells release VEGF-A and FGF-2 [18], and mast cell supernatants induce an angiogenic response in the chorioallantoic membrane [19][20]. HLMCs constitutively express other VEGFs in addition to VEGF-A, namely the angiogenic VEGF-B and the lymphangiogenic VEGF-C and -D [21]. These VEGFs are often present as preformed mediators in mast cells [22]. PGE₂ and adenosine, two important proinflammatory mediators, induced the expression of VEGF-A, -C, and -D in HLMCs [21]. These findings indicate that HLMCs have an intrinsic capacity to produce several VEGFs, suggesting that these cells might regulate both angiogenesis and lymphangiogenesis. HLMCs are not only a source of VEGFs in the airways, but also a target for these angiogenic factors. Indeed, HLMCs express VEGFR1 and 2, two major receptors for VEGFs. Different VEGFs (VEGF-A, -B, -C, -D, and PlGF-1) exert chemotactic effects on HLMCs by engaging both receptors.

3. Neutrophils

Increased numbers of activated neutrophils are found in the sputum and BAL fluid of COPD patients and correlate with disease severity, although few neutrophils are found in the bronchial wall and lung parenchyma [23]. Smoking stimulates the production and release of neutrophils from bone marrow and survival in the respiratory tract, possibly mediated by GM-CSF and G-CSF secreted from lung macrophages. Neutrophils' recruitment to the lung parenchyma involves initial adhesion to activated ECs through E-selectin, which is overexpressed on ECs in the airways of COPD patients. Neutrophils migrate into the respiratory tract under various chemotactic factors such as LTB₄, CXCL1, CXCL5, and CXCL8 [24]. These chemotactic mediators can be derived from alveolar macrophages, mast cells, T cells, and epithelial cells [24]. Neutrophils themselves might be a major source of CXCL8 [25]. Neutrophils from COPD patients are activated and have increased concentrations of myeloperoxidase [19][26]. Activated neutrophils secrete neutrophil elastase (NE), cathepsin G (CG), and proteinase 3 (PR3), as well as MMP-8 and MMP-9, which contribute to alveolar destruction. NE, CG, and PR3 are potent promoters of mucus secretion from submucosal glands and goblet cells [27]. During COPD exacerbations, there is a marked increase of neutrophils in the airways, resulting in the increased production of neutrophil chemotactic factors (e.g., LTB₄ and CXCL8) [28].

Activated human neutrophils release neutrophil extracellular traps (NETs) [29][30]. Increased components of NETs have been found in the sputum of both stable and exacerbating COPD patients, alongside an increased proportion of NET-producing neutrophils [31][32]. The abundance of NETs in sputum correlates with the severity of airflow limitation [31][33], loss of microbiota diversity [33], and overall severity of COPD [33]. Despite these observations, neutrophils isolated from the blood of patients with COPD exacerbations have an apparently reduced ability to form NETs compared to stable patients and healthy controls, despite the increased plasma levels of cell-free DNA [34]. Finally, it should be noted that NETs can directly and indirectly promote angiogenesis [35].

Human neutrophils constitutively express and contain several proangiogenic factors (VEGF-A₁₆₅, VEGF-B, ANGPT1, CXCL8, and HGF) [36][37]. Human neutrophils, similarly to other circulating immune cells (e.g., basophils) [38], do not express lymphangiogenic factors (VEGF-C and -D). sPLA₂ selectively induces the release of proangiogenic factors from human neutrophils [36]. Of note, sPLA₂-activated neutrophils also express the antiangiogenic isoform VEGF_{165b} [36]. The relevance of the latter observation in the context of COPD remains to be defined.

4. Eosinophils

Eosinophils have been identified in different anatomical compartments of COPD-affected lungs and increased in severe patients [39]. However, the role of eosinophils and their mediators in COPD is still uncertain. Increased eosinophil numbers have been described in the airways and BAL fluid of patients with stable COPD, whereas others have not found increased numbers in airway biopsies, BAL fluid, or induced sputum [40]. The presence of eosinophils in COPD patients seems to predict a more favorable therapeutic response to bronchodilators and ICS [41] and might indicate coexisting asthma or asthma-COPD overlap syndrome (ACOS) [42][43][44]. Up to 15% of COPD patients appear to have clinical features of asthma [19]. The mechanism for increased eosinophil counts in some patients with COPD is debated [45]. It has been suggested that damaged BECs release IL-33, which can induce the release of IL-5 from ILC2s [46]. IL-33 expression is increased in basal epithelial progenitor cells in COPD patients and is associated with increased levels of IL-13 and the mucin gene 5AC [47]. IL-33 is expressed in the lungs of COPD patients [48], and levels of IL-33 and its receptors ST2 are increased in the serum of these patients. Moreover, circulating IL-33 levels in COPD patients are correlated to peripheral blood eosinophils [49]. Finally, the exposure of PBMCs from COPD patients to combustion-generated ultrafine particles obtained from fuel induced the release of IL-33 [50].

The potential role of eosinophils and their powerful mediators in the pathophysiology of certain COPD endotypes has generated some enthusiasm in treating this heterogeneous disorder with monoclonal antibodies (mAbs) targeting IL-5 (i.e., mepolizumab) or IL-5R α (i.e., benralizumab). In COPD patients with eosinophilic phenotype, mepolizumab decreased the annual rate of exacerbations compared to a placebo group [51]. Benralizumab was not associated with a lower annualized rate of COPD exacerbations than placebo among patients with blood eosinophils counts ≥ 220 per mm³ [52].

Human eosinophils synthesize and store in their granules several proangiogenic mediators such as VEGF-A, FGF-2, TNF- α , GM-CSF, nerve growth factor (NGF), and CXCL8 [53]. In addition, these cells promote EC proliferation in vitro and induce vessel formation in aortic rings and in the chick CAM assays [54].

5. Basophils

Although human basophils account for 0.5–1% of all leukocytes in peripheral blood, these cells play critical roles in clearing pathogens [55][56][57], initiating allergic disorders [58][59], and COPD [39]. Basophil density is increased in the

lung tissue of COPD patients compared to smoking controls [39]. A significant correlation was found between basophils and eosinophils in the lungs of COPD patients. Activated human basophils express several forms of VEGF-A (121, 165, 189), and their secretory granules contain VEGF-A [38]. The activation of human basophils induces the release of VEGF-A [38] and ANGPT1 [60]. Human basophils also express HGF [61]. VEGF-A has a chemotactic effect on basophils through the activation of VEGFR2. These cells do not express VEGF-C and -D and presumably play a role in angiogenesis, but not in lymphangiogenesis [38].

6. Lymphocytes

CD8⁺ and, to a lesser extent, CD4⁺ T cells, are increased in the lung parenchyma, bronchi, and bronchioles of COPD patients compared to asymptomatic smokers [62][63]. There is evidence that CD8⁺ T lymphocytes are both increased in number and have increased functional activity in COPD [63]. CXCR3 is highly expressed on effector T cells following activation by ligands such as CXCL10. CD8⁺ T lymphocytes themselves produce CXCL10, thus recruiting more CXCR3⁺ T cells to the lung, where they exert inflammatory and destructive effects. The overexpression of CXCR3 and its ligand CXCL10 by BECs could contribute to the accumulation of CD8⁺ and CD4⁺ T cells, which express CXCR3 [64].

ILCs are critical players in mucosal immunity. Group 1 ILCs (ILC1), group 2 (ILC2), and group 3 (ILC3) are a population of tissue-resident lymphocytes with pleiotropic roles in mucosal inflammation, including defense against pathogens, the maintenance of epithelial barrier homeostasis, the containment of microbiota, and tissue repair [65]. ILCs play an important role in the regulation of lung immunity and might be activated through danger signals and cell damage [66]. All three groups of ILCs have been identified in the human lung [67]. In COPD patients, there is an increase in the number of ILC3s, which secrete IL-17 and IL-22, and these cells might play a role in driving neutrophilic inflammation. Exposure to cigarette smoke inhibits ILC2 function, and this is associated with an exaggerated anti-viral response [68]. Moreover, exposure to cigarette smoke and viral infections induced the emergence of the ILC1 population in mice [69]. The same authors found that the frequency of circulating ILC1 was higher in COPD patients compared to healthy controls. Conversely, the frequency of ILC2 cells was lower in COPD patients compared to healthy smokers. A similar increase in ILC1 frequency has been reported in the lungs of COPD patients [70].

A distinct cluster of CD4⁺ T helper 17 (Th17) cells are characterized by the expression of the master transcription factor RORγt [71]. CD4⁺ T_H17 cells, which secrete IL-17A and IL-22, are increased in the airways of COPD patients and might play a role in orchestrating neutrophilic inflammation [72][73]. Th17 cells produce the IL-17 family of structurally related cytokines, IL-17A through IL-17F. IL-17A, commonly known as IL-17, is the prototypical member of this family. It was reported that Th17 cells release IL-1β and IL-17 and exert lymphangiogenic effects [74]. IL-17A promotes angiogenesis in preclinical [75] and clinical models of vascular remodeling [76]. IL-17E (IL-25), a little unusual among the IL-17 family, is produced by bronchial epithelial cells [77] and tuft cells [78] and in respiratory viral infections [79].

B lymphocytes are also increased in the lungs of COPD patients, particularly in those with severe disease [80]. B cells can be organized into lymphoid follicles located in peripheral airways and lung parenchyma [81]. The expression of B-cell activating factor, an important regulator of B-cell function and hyperplasia, is increased in the lymphoid follicles of patients with COPD [82][83]. Recent evidence indicates that a subset of regulatory B cells (Bregs) with high levels of the surface markers CD24 and CD38, previously shown to exert immunosuppressive functions, is decreased in the peripheral blood of COPD patients [84].

7. Dendritic Cells

Dendritic cells (DCs) are an important link between innate and adaptive immunity [85]. The airways and lungs contain a rich network of DCs localized near the surface, so that they are ideally located to signal the entry of inhaled foreign substances [86][87]. Epithelium-derived cytokines (TSLP, IL-33, IL-25) are important modulators of DC functions [88][89][90]. DCs can activate a variety of other inflammatory and immune cells, including macrophages, neutrophils, and T and B lymphocytes, and therefore DCs might play an important role in the pulmonary response to cigarette smoke and other inhaled toxic chemicals [91]. DCs are activated in the lungs of COPD patients [92] and correlate to disease severity [93]. The numbers of DCs are increased in the lungs of COPD patients, and cigarette smoke increases their survival in vitro [94]. Human DCs can produce biologically active VEGF-A [85]. DCs activated by different bacteria release VEGF-A, which induces neutrophil recruitment to the site of inflammation [95].

8. NK Cells

NK cells, as innate immune cells, contribute to the first line of defense mechanisms for the human body against viral and bacterial infections and tumors [96]. NK cells have been implicated in maintaining immune homeostasis in the lung and in the pathogenesis of COPD [97][98]. However, the specific mechanisms of involvement of NK cells in COPD are still rather elusive [99]. NK cells make up 5–15% of the circulating lymphocytes. These cells are subdivided into two main subpopulations, CD56^{bright} CD16⁻ and CD56^{dim} CD16⁺. CD56^{bright} CD16⁻ NK cells, accounting for about 10% of peripheral blood NK population, mainly produce several cytokines (i.e., IFN- γ , IL-10, TNF- α , GM-CSF). CD56^{dim} CD16⁺ NK cells, the predominant (approximately 90%) peripheral blood NK cells, are highly cytotoxic by producing perforin and granzymes and inducing antibody-dependent cytotoxicity [96]. In humans, NK cells represent 5-20% of the CD45⁺ lung lymphocytes [100]. Approximately 80% of lung NK cells show the CD56^{dim} CD16⁺ phenotype, whereas the remaining 20% are CD56^{bright} CD16⁻ and CD56^{dim} CD16⁻ [98]. There is evidence that the low cytotoxic CD56^{bright} CD16⁻ phenotype exerts pro-angiogenic activity [101].

Several studies examining the frequency and activation status of NK cells in peripheral blood and induced sputum in COPD patients have provided contrasting results [99]. Thus, further studies are needed to elucidate the mechanisms of NK cells in the pathogenesis, endotypes, and exacerbations of COPD.

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