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), γδ 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.

Keywords: 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, LTB_4], 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 A_2 ($sPLA_2$), 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]. PGE_2 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 LTB_4, 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., LTB_4 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-A_{165}, 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). $sPLA_2$ selectively induces the release of proangiogenic factors from human neutrophils [36]. Of note, $sPLA_2$-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-5Rα (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 mm^3 [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.

References

1. Braile, M.; Fiorelli, A.; Sorriento, D.; di Crescenzo, R.M.; Galdiero, M.R.; Marone, G.; Santini, M.; Varricchi, G.; Loffredo, S. Human Lung-Resident Macrophages Express and Are Targets of Thymic Stromal Lymphopoietin in the Tumor Microenvironment. Cells 2021, 10, 2012.
2. Staiano, R.I.; Loffredo, S.; Borriello, F.; Iannotti, F.A.; Piscitelli, F.; Orlando, P.; Secondo, A.; Granata, F.; Lepore, M.T.; Fiorelli, A.; et al. Human Lung-Resident Macrophages Express Cb1 and Cb2 Receptors Whose Activation Inhibits the Release of Angiogenic and Lymphangiogenic Factors. J. Leukoc. Biol. 2016, 99, 531–540.
3. Russell, R.E.; Thorley, A.; Culpitt, S.V.; Dodd, S.; Donnelly, L.E.; Demattos, C.; Fitzgerald, M.; Barnes, P.J. Alveolar Macrophage-Mediated Elastolysis: Roles of Matrix Metalloproteinases, Cysteine, and Serine Proteases. Am. J. Physiol. Lung Cell Mol. Physiol. 2002, 283, L867–L873.
4. Chevrier, S.; Levine, J.H.; Zanotelli, V.R.T.; Silina, K.; Schulz, D.; Bacac, M.; Ries, C.H.; Ailles, L.; Jewett, M.A.S.; Moch, H.; et al. An Immune Atlas of Clear Cell Renal Cell Carcinoma. Cell 2017, 169, 736–749.e18.
5. Lavin, Y.; Kobayashi, S.; Leader, A.; Amir, E.D.; Elefant, N.; Bigenwald, C.; Remark, R.; Sweeney, R.; Becker, C.D.; Levine, J.H.; et al. Innate Immune Landscape in Early Lung Adenocarcinoma by Paired Single-Cell Analyses. Cell 2017, 169, 750–765.e17.
6. Zilionis, R.; Engblom, C.; Pfirschke, C.; Savova, V.; Zemmour, D.; Saatcioglu, H.D.; Krishnan, I.; Maroni, G.; Meyerovitz, C.V.; Kerwin, C.M.; et al. Single-Cell Transcriptomics of Human and Mouse Lung Cancers Reveals Conserved Myeloid Populations across Individuals and Species. Immunity 2019, 50, 1317–1334.e10.
7. Vieira Braga, F.A.; Kar, G.; Berg, M.; Carpaij, O.A.; Polanski, K.; Simon, L.M.; Brouwer, S.; Gomes, T.; Hesse, L.; Jiang, J.; et al. A Cellular Census of Human Lungs Identifies Novel Cell States in Health and in Asthma. Nat. Med. 2019, 25, 1153–1163.
8. Hua, X.; Hu, G.; Hu, Q.; Chang, Y.; Hu, Y.; Gao, L.; Chen, X.; Yang, P.C.; Zhang, Y.; Li, M.; et al. Single-Cell Rna Sequencing to Dissect the Immunological Network of Autoimmune Myocarditis. Circulation 2020, 142, 384–400.
9. Balestrieri, B.; Granata, F.; Loffredo, S.; Petraroli, A.; Scalia, G.; Morabito, P.; Cardamone, C.; Varricchi, G.; Triggiani, M. Phenotypic and Functional Heterogeneity of Low-Density and High-Density Human Lung Macrophages. Biomedicines 2021, 9, 505.
10. Chana, K.K.; Fenwick, P.S.; Nicholson, A.G.; Barnes, P.J.; Donnelly, L.E. Identification of a Distinct Glucocorticosteroid-Insensitive Pulmonary Macrophage Phenotype in Patients with Chronic Obstructive Pulmonary Disease. J. Allergy Clin. Immunol. 2014, 133, 207–216.e11.
11. Finney, L.J.; Belchamber, K.B.R.; Fenwick, P.S.; Kemp, S.V.; Edwards, M.R.; Mallia, P.; Donaldson, G.; Johnston, S.L.; Donnelly, L.E.; Wedzicha, J.A. Human Rhinovirus Impairs the Innate Immune Response to Bacteria in Alveolar Macrophages in Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2019, 199, 1496–1507.
12. Granata, F.; Frattini, A.; Loffredo, S.; Staiano, R.I.; Petraroli, A.; Ribatti, D.; Oslund, R.; Gelb, M.H.; Lambeau, G.; Marone, G.; et al. Production of Vascular Endothelial Growth Factors from Human Lung Macrophages Induced by Group Iia and Group X Secreted Phospholipases A2. J. Immunol. 2010, 184, 5232–5241.

13. Granata, F.; Balestrieri, B.; Petraroli, A.; Giannattasio, G.; Marone, G.; Triggiani, M. Secretory Phospholipases A2 as Multivalent Mediators of Inflammatory and Allergic Disorders. Int. Arch. Allergy Immunol. 2003, 131, 153–163.
14. Varricchi, G.; Loffredo, S.; Borriello, F.; Pecoraro, A.; Rivellese, F.; Genovese, A.; Spadaro, G.; Marone, G. Superantigenic Activation of Human Cardiac Mast Cells. Int. J. Mol. Sci. 2019, 20, 1828.
15. Varricchi, G.; de Paulis, A.; Marone, G.; Galli, S.J. Future Needs in Mast Cell Biology. Int. J. Mol. Sci. 2019, 20, 4397.
16. Plum, T.; Wang, X.; Rettel, M.; Krijgsveld, J.; Feyerabend, T.B.; Rodewald, H.R. Human Mast Cell Proteome Reveals Unique Lineage, Putative Functions, and Structural Basis for Cell Ablation. Immunity 2020, 52, 404–416.e5.
17. Soltani, A.; Ewe, Y.P.; Lim, Z.S.; Sohal, S.S.; Reid, D.; Weston, S.; Wood-Baker, R.; Walters, E.H. Mast Cells in Copd Airways: Relationship to Bronchodilator Responsiveness and Angiogenesis. Eur. Respir. J. 2012, 39, 1361–1367.
18. Boesiger, J.; Tsai, M.; Maurer, M.; Yamaguchi, M.; Brown, L.F.; Claffey, K.P.; Dvorak, H.F.; Galli, S.J. Mast Cells Can Secrete Vascular Permeability Factor/Vascular Endothelial Cell Growth Factor and Exhibit Enhanced Release after Immunoglobulin E-Dependent Upregulation of Fc Epsilon Receptor I Expression. J. Exp. Med. 1998, 188, 1135–1145.
19. Cosio, B.G.; Soriano, J.B.; Lopez-Campos, J.L.; Calle-Rubio, M.; Soler-Cataluna, J.J.; de-Torres, J.P.; Marin, J.M.; Martinez-Gonzalez, C.; de Lucas, P.; Mir, I.; et al. Defining the Asthma-Copd Overlap Syndrome in a Copd Cohort. Chest 2016, 149, 45–52.
20. Ribatti, D.; Crivellato, E.; Candussio, L.; Nico, B.; Vacca, A.; Roncali, L.; Dammacco, F. Mast Cells and Their Secretory Granules Are Angiogenic in the Chick Embryo Chorioallantoic Membrane. Clin. Exp. Allergy 2001, 31, 602–608.
21. Detoraki, A.; Staiano, R.I.; Granata, F.; Giannattasio, G.; Prevete, N.; de Paulis, A.; Ribatti, D.; Genovese, A.; Triggiani, M.; Marone, G. Vascular Endothelial Growth Factors Synthesized by Human Lung Mast Cells Exert Angiogenic Effects. J. Allergy Clin. Immunol. 2009, 123, 1142–1149.e5.
22. Marcella, S.; Petraroli, A.; Braile, M.; Parente, R.; Ferrara, A.L.; Galdiero, M.R.; Modestino, L.; Cristinziano, L.; Rossi, F.W.; Varricchi, G.; et al. Vascular Endothelial Growth Factors and Angiopoietins as New Players in Mastocytosis. Clin. Exp. Med. 2021, 21, 415–427.
23. Jasper, A.E.; McIver, W.J.; Sapey, E.; Walton, G.M. Understanding the Role of Neutrophils in Chronic Inflammatory Airway Disease. F1000Research 2019, 8.
24. Miralda, I.; Uriarte, S.M.; McLeish, K.R. Multiple Phenotypic Changes Define Neutrophil Priming. Front. Cell Infect. Microbiol. 2017, 7, 217.
25. Braile, M.; Cristinziano, L.; Marcella, S.; Varricchi, G.; Marone, G.; Modestino, L.; Ferrara, A.L.; de Ciuceis, A.; Scala, S.; Galdiero, M.R.; et al. Lps-Mediated Neutrophil Vegf-a Release Is Modulated by Cannabinoid Receptor Activation. J. Leukoc. Biol. 2021, 109, 621–631.
26. Keatings, V.M.; Barnes, P.J. Granulocyte Activation Markers in Induced Sputum: Comparison between Chronic Obstructive Pulmonary Disease, Asthma, and Normal Subjects. Am. J. Respir. Crit. Care Med. 1997, 155, 449–453.
27. Fahy, J.V.; Dickey, B.F. Airway Mucus Function and Dysfunction. N. Engl. J. Med. 2010, 363, 2233–2247.
28. Biernacki, W.A.; Kharitonov, S.A.; Barnes, P.J. Increased Leukotriene B4 and 8-Isoprostane in Exhaled Breath Condensate of Patients with Exacerbations of Copd. Thorax 2003, 58, 294–298.
29. Cristinziano, L.; Modestino, L.; Loffredo, S.; Varricchi, G.; Braile, M.; Ferrara, A.L.; de Paulis, A.; Antonelli, A.; Marone, G.; Galdiero, M.R. Anaplastic Thyroid Cancer Cells Induce the Release of Mitochondrial Extracellular DNA Traps by Viable Neutrophils. J. Immunol. 2020, 204, 1362–1372.
30. Varricchi, G.; Modestino, L.; Poto, R.; Cristinziano, L.; Gentile, L.; Postiglione, L.; Spadaro, G.; Galdiero, M.R. Neutrophil Extracellular Traps and Neutrophil-Derived Mediators as Possible Biomarkers in Bronchial Asthma. Clin. Exp. Med. 2021, 22, 285–300.
31. Grabcanovic-Musija, F.; Obermayer, A.; Stoiber, W.; Krautgartner, W.D.; Steinbacher, P.; Winterberg, N.; Bathke, A.C.; Klappacher, M.; Studnicka, M. Neutrophil Extracellular Trap (Net) Formation Characterises Stable and Exacerbated Copd and Correlates with Airflow Limitation. Respir. Res. 2015, 16, 59.
32. Obermayer, A.; Stoiber, W.; Krautgartner, W.D.; Klappacher, M.; Kofler, B.; Steinbacher, P.; Vitkov, L.; Grabcanovic-Musija, F.; Studnicka, M. New Aspects on the Structure of Neutrophil Extracellular Traps from Chronic Obstructive Pulmonary Disease and in Vitro Generation. PLoS ONE 2014, 9, e97784.
33. Dicker, A.J.; Crichton, M.L.; Pumphrey, E.G.; Cassidy, A.J.; Suarez-Cuartin, G.; Sibila, O.; Furrie, E.; Fong, C.J.; Ibrahim, W.; Brady, G.; et al. Neutrophil Extracellular Traps Are Associated with Disease Severity and Microbiota Diversity in Patients with Chronic Obstructive Pulmonary Disease. J. Allergy Clin. Immunol. 2018, 141, 117–127.
34. Pullan, J.; Greenwood, H.; Walton, G.M.; Stockley, R.A.; Sapey, E. Neutrophil Extracellular Traps (Nets) in Copd: A Potential Novel Mechanism for Host Damage in Acute Exacerbations. Eur. Respir. J. 2015, 46, PA5055.

35. Poto, R.; Cristinziano, L.; Modestino, L.; de Paulis, A.; Marone, G.; Loffredo, S.; Galdiero, M.R.; Varricchi, G. Neutrophil Extracellular Traps, Angiogenesis and Cancer. Biomedicines 2022, 10, 431.

36. Loffredo, S.; Borriello, F.; Iannone, R.; Ferrara, A.L.; Galdiero, M.R.; Gigantino, V.; Esposito, P.; Varricchi, G.; Lambeau, G.; Cassatella, M.A.; et al. Group V Secreted Phospholipase A2 Induces the Release of Proangiogenic and Antiangiogenic Factors by Human Neutrophils. Front. Immunol. 2017, 8, 443.

37. Ilangumaran, S.; Villalobos-Hernandez, A.; Bobbala, D.; Ramanathan, S. The Hepatocyte Growth Factor (Hgf)-Met Receptor Tyrosine Kinase Signaling Pathway: Diverse Roles in Modulating Immune Cell Functions. Cytokine 2016, 82, 125–139.

38. De Paulis, A.; Prevete, N.; Fiorentino, I.; Rossi, F.W.; Staibano, S.; Montuori, N.; Ragno, P.; Longobardi, A.; Liccardo, B.; Genovese, A.; et al. Expression and Functions of the Vascular Endothelial Growth Factors and Their Receptors in Human Basophils. J. Immunol. 2006, 177, 7322–7331.

39. Jogdand, P.; Siddhuraj, P.; Mori, M.; Sanden, C.; Jonsson, J.; Walls, A.F.; Kearley, J.; Humbles, A.A.; Kolbeck, R.; Bjermer, L.; et al. Eosinophils, Basophils and Type 2 Immune Microenvironments in Copd-Affected Lung Tissue. Eur. Respir. J. 2020, 55, 1900110.

40. Barnes, P.J. Role of Hdac2 in the Pathophysiology of Copd. Annu. Rev. Physiol. 2009, 71, 451–464.

41. Singh, D.; Bafadhel, M.; Brightling, C.E.; Sciurba, F.C.; Curtis, J.L.; Martinez, F.J.; Pasquale, C.B.; Merrill, D.D.; Metzdorf, N.; Petruzzelli, S.; et al. Blood Eosinophil Counts in Clinical Trials for Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2020, 202, 660–671.

42. Postma, D.S.; Rabe, K.F. The Asthma-Copd Overlap Syndrome. N. Engl. J. Med. 2015, 373, 1241–1249.

43. Bateman, E.D.; Reddel, H.K.; van Zyl-Smit, R.N.; Agusti, A. The Asthma-Copd Overlap Syndrome: Towards a Revised Taxonomy of Chronic Airways Diseases? Lancet Respir. Med. 2015, 3, 719–728.

44. Barnes, P.J. Asthma-Copd Overlap. Chest 2016, 149, 7–8.

45. Lee, L.Y.; Hew, G.S.Y.; Mehta, M.; Shukla, S.D.; Satija, S.; Khurana, N.; Anand, K.; Dureja, H.; Singh, S.K.; Mishra, V.; et al. Targeting Eosinophils in Respiratory Diseases: Biological Axis, Emerging Therapeutics and Treatment Modalities. Life Sci. 2021, 267, 118973.

46. De Kleer, I.M.; Kool, M.; de Bruijn, M.J.; Willart, M.; van Moorleghem, J.; Schuijs, M.J.; Plantinga, M.; Beyaert, R.; Hams, E.; Fallon, P.G.; et al. Perinatal Activation of the Interleukin-33 Pathway Promotes Type 2 Immunity in the Developing Lung. Immunity 2016, 45, 1285–1298.

47. Byers, D.E.; Alexander-Brett, J.; Patel, A.C.; Agapov, E.; Dang-Vu, G.; Jin, X.; Wu, K.; You, Y.; Alevy, Y.; Girard, J.P.; et al. Long-Term Il-33-Producing Epithelial Progenitor Cells in Chronic Obstructive Lung Disease. J. Clin. Investig. 2013, 123, 3967–3982.

48. Xia, J.; Zhao, J.; Shang, J.; Li, M.; Zeng, Z.; Zhao, J.; Wang, J.; Xu, Y.; Xie, J. Increased Il-33 Expression in Chronic Obstructive Pulmonary Disease. Am. J. Physiol. Lung Cell Mol. Physiol. 2015, 308, L619–L627.

49. Kim, S.W.; Rhee, C.K.; Kim, K.U.; Lee, S.H.; Hwang, H.G.; Kim, Y.I.; Kim, D.K.; Lee, S.D.; Oh, Y.M.; Yoon, H.K. Factors Associated with Plasma Il-33 Levels in Patients with Chronic Obstructive Pulmonary Disease. Int. J. Chron. Obstruct. Pulmon. Dis. 2017, 12, 395–402.

50. De Falco, G.; Colarusso, C.; Terlizzi, M.; Popolo, A.; Pecoraro, M.; Commodo, M.; Minutolo, P.; Sirignano, M.; D'Anna, A.; Aquino, R.P.; et al. Chronic Obstructive Pulmonary Disease-Derived Circulating Cells Release Il-18 and Il-33 under Ultrafine Particulate Matter Exposure in a Caspase-1/8-Independent Manner. Front. Immunol. 2017, 8, 1415.

51. Pavord, I.D.; Chanez, P.; Criner, G.J.; Kerstjens, H.A.M.; Korn, S.; Lugogo, N.; Martinot, J.B.; Sagara, H.; Albers, F.C.; Bradford, E.S.; et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N. Engl. J. Med. 2017, 377, 1613–1629.

52. Criner, G.J.; Celli, B.R.; Brightling, C.E.; Agusti, A.; Papi, A.; Singh, D.; Sin, D.D.; Vogelmeier, C.F.; Sciurba, F.C.; Bafadhel, M.; et al. Benralizumab for the Prevention of Copd Exacerbations. N. Engl. J. Med. 2019, 381, 1023–1034.

53. Puxeddu, I.; Berkman, N.; Efraim, A.H.N.B.; Davies, D.E.; Ribatti, D.; Gleich, G.J.; Levi-Schaffer, F. The Role of Eosinophil Major Basic Protein in Angiogenesis. Allergy 2009, 64, 368–374.

54. Puxeddu, I.; Alian, A.; Piliponsky, A.M.; Ribatti, D.; Panet, A.; Levi-Schaffer, F. Human Peripheral Blood Eosinophils Induce Angiogenesis. Int. J. Biochem. Cell Biol. 2005, 37, 628–636.

55. Rivellese, F.; Suurmond, J.; de Paulis, A.; Marone, G.; Huizinga, T.W.; Toes, R.E. Ige and Il-33-Mediated Triggering of Human Basophils Inhibits Tlr4-Induced Monocyte Activation. Eur. J. Immunol. 2014, 44, 3045–3055.

56. Galli, S.J. Mast Cells and Basophils. Curr. Opin. Hematol. 2000, 7, 32–39.

57. Siracusa, M.C.; Kim, B.S.; Spergel, J.M.; Artis, D. Basophils and Allergic Inflammation. J. Allergy Clin. Immunol. 2013, 132, 789–801.

58. Marone, G.; Borriello, F.; Varricchi, G.; Genovese, A.; Granata, F. Basophils: Historical Reflections and Perspectives. Chem. Immunol. Allergy 2014, 100, 172–192.

59. Varricchi, G.; Raap, U.; Rivellese, F.; Marone, G.; Gibbs, B.F. Human Mast Cells and Basophils-How Are They Similar How Are They Different? Immunol. Rev. 2018, 282, 8–34.

60. Prevete, N.; Staiano, R.I.; Granata, F.; Detoraki, A.; Necchi, V.; Ricci, V.; Triggiani, M.; de Paulis, A.; Marone, G.; Genovese, A. Expression and Function of Angiopoietins and Their Tie Receptors in Human Basophils and Mast Cells. J. Biol. Regul. Homeost. Agents 2013, 27, 827–839.

61. Cerny-Reiterer, S.; Ghanim, V.; Hoermann, G.; Aichberger, K.J.; Herrmann, H.; Muellauer, L.; Repa, A.; Sillaber, C.; Walls, A.F.; Mayerhofer, M.; et al. Identification of Basophils as a Major Source of Hepatocyte Growth Factor in Chronic Myeloid Leukemia: A Novel Mechanism of Bcr-Abl1-Independent Disease Progression. Neoplasia 2012, 14, 572–584.

62. Saetta, M.; di Stefano, A.; Turato, G.; Facchini, F.M.; Corbino, L.; Mapp, C.E.; Maestrelli, P.; Ciaccia, A.; Fabbri, L.M. Cd8+ T-Lymphocytes in Peripheral Airways of Smokers with Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 1998, 157, 822–826.

63. Williams, M.; Todd, I.; Fairclough, L.C. The Role of Cd8+ T Lymphocytes in Chronic Obstructive Pulmonary Disease: A Systematic Review. Inflamm. Res. 2021, 70, 11–18.

64. Saetta, M.; Mariani, M.; Panina-Bordignon, P.; Turato, G.; Buonsanti, C.; Baraldo, S.; Bellettato, C.M.; Papi, A.; Corbetta, L.; Zuin, R.; et al. Increased Expression of the Chemokine Receptor Cxcr3 and Its Ligand Cxcl10 in Peripheral Airways of Smokers with Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2002, 165, 1404–1409.

65. Ebbo, M.; Crinier, A.; Vely, F.; Vivier, E. Innate Lymphoid Cells: Major Players in Inflammatory Diseases. Nat. Rev. Immunol. 2017, 17, 665–678.

66. Artis, D.; Spits, H. The Biology of Innate Lymphoid Cells. Nature 2015, 517, 293–301.

67. De Grove, K.C.; Provoost, S.; Verhamme, F.M.; Bracke, K.R.; Joos, G.F.; Maes, T.; Brusselle, G.G. Characterization and Quantification of Innate Lymphoid Cell Subsets in Human Lung. PLoS ONE 2016, 11, e0145961.

68. Kearley, J.; Silver, J.S.; Sanden, C.; Liu, Z.; Berlin, A.A.; White, N.; Mori, M.; Pham, T.H.; Ward, C.K.; Criner, G.J.; et al. Cigarette Smoke Silences Innate Lymphoid Cell Function and Facilitates an Exacerbated Type I Interleukin-33-Dependent Response to Infection. Immunity 2015, 42, 566–579.

69. Silver, J.S.; Kearley, J.; Copenhaver, A.M.; Sanden, C.; Mori, M.; Yu, L.; Pritchard, G.H.; Berlin, A.A.; Hunter, C.A.; Bowler, R.; et al. Inflammatory Triggers Associated with Exacerbations of Copd Orchestrate Plasticity of Group 2 Innate Lymphoid Cells in the Lungs. Nat. Immunol. 2016, 17, 626–635.

70. Bal, S.M.; Bernink, J.H.; Nagasawa, M.; Groot, J.; Shikhagaie, M.M.; Golebski, K.; van Drunen, C.M.; Lutter, R.; Jonkers, R.E.; Hombrink, P.; et al. Il-1beta, Il-4 and Il-12 Control the Fate of Group 2 Innate Lymphoid Cells in Human Airway Inflammation in the Lungs. Nat. Immunol. 2016, 17, 636–645.

71. McGeachy, M.J.; Cua, D.J.; Gaffen, S.L. The Il-17 Family of Cytokines in Health and Disease. Immunity 2019, 50, 892–906.

72. Di Stefano, A.; Caramori, G.; Gnemmi, I.; Contoli, M.; Vicari, C.; Capelli, A.; Magno, F.; D'Anna, S.E.; Zanini, A.; Brun, P.; et al. T Helper Type 17-Related Cytokine Expression Is Increased in the Bronchial Mucosa of Stable Chronic Obstructive Pulmonary Disease Patients. Clin. Exp. Immunol. 2009, 157, 316–324.

73. Pridgeon, C.; Bugeon, L.; Donnelly, L.; Straschil, U.; Tudhope, S.J.; Fenwick, P.; Lamb, J.R.; Barnes, P.J.; Dallman, M.J. Regulation of Il-17 in Chronic Inflammation in the Human Lung. Clin. Sci. 2011, 120, 515–524.

74. Chauhan, S.K.; Jin, Y.; Goyal, S.; Lee, H.S.; Fuchsluger, T.A.; Lee, H.K.; Dana, R. A Novel Pro-Lymphangiogenic Function for Th17/Il-17. Blood 2011, 118, 4630–4634.

75. Numasaki, M.; Fukushi, J.; Ono, M.; Narula, S.K.; Zavodny, P.J.; Kudo, T.; Robbins, P.D.; Tahara, H.; Lotze, M.T. Interleukin-17 Promotes Angiogenesis and Tumor Growth. Blood 2003, 101, 2620–2627.

76. Panariti, A.; Baglole, C.J.; Sanchez, V.; Eidelman, D.H.; Hussain, S.; Olivenstein, R.; Martin, J.G.; Hamid, Q. Interleukin-17a and Vascular Remodelling in Severe Asthma; Lack of Evidence for a Direct Role. Clin. Exp. Allergy 2018, 48, 365–378.

77. Wang, W.; Li, Y.; Lv, Z.; Chen, Y.; Huang, K.; Corrigan, C.J.; Ying, S. Bronchial Allergen Challenge of Patients with Atopic Asthma Triggers an Alarmin (Il-33, Tslp, and Il-25) Response in the Airways Epithelium and Submucosa. J. Immunol. 2018, 201, 2221–2231.

78. Kohanski, M.A.; Workman, A.D.; Patel, N.N.; Hung, L.Y.; Shtraks, J.P.; Chen, B.; Blasetti, M.; Doghramji, L.; Kennedy, D.W.; Adappa, N.D.; et al. Solitary Chemosensory Cells Are a Primary Epithelial Source of Il-25 in Patients with Chronic Rhinosinusitis with Nasal Polyps. J. Allergy Clin. Immunol. 2018, 142, 460–469.e7.

79. Beale, J.; Jayaraman, A.; Jackson, D.J.; Macintyre, J.D.R.; Edwards, M.R.; Walton, R.P.; Zhu, J.; Ching, Y.M.; Shamji, B.; Edwards, M.; et al. Rhinovirus-Induced Il-25 in Asthma Exacerbation Drives Type 2 Immunity and Allergic Pulmonary Inflammation. Sci. Transl. Med. 2014, 6, 256ra134.

80. Polverino, F.; Baraldo, S.; Bazzan, E.; Agostini, S.; Turato, G.; Lunardi, F.; Balestro, E.; Damin, M.; Papi, A.; Maestrelli, P.; et al. A Novel Insight into Adaptive Immunity in Chronic Obstructive Pulmonary Disease: B Cell Activating Factor Belonging to the Tumor Necrosis Factor Family. Am. J. Respir. Crit. Care Med. 2010, 182, 1011–1019.

81. Hogg, J.C.; Chu, F.; Utokaparch, S.; Woods, R.; Elliott, W.M.; Buzatu, L.; Cherniack, R.M.; Rogers, R.M.; Sciurba, F.C.; Coxson, H.O.; et al. The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease. N. Engl. J. Med. 2004, 350, 2645–2653.

82. Seys, L.J.; Verhamme, F.M.; Schinwald, A.; Hammad, H.; Cunoosamy, D.M.; Bantsimba-Malanda, C.; Sabirsh, A.; McCall, E.; Flavell, L.; Herbst, R.; et al. Role of B Cell-Activating Factor in Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2015, 192, 706–718.

83. Polverino, F.; Cosio, B.G.; Pons, J.; Laucho-Contreras, M.; Tejera, P.; Iglesias, A.; Rios, A.; Jahn, A.; Sauleda, J.; Divo, M.; et al. B Cell-Activating Factor. An Orchestrator of Lymphoid Follicles in Severe Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2015, 192, 695–705.

84. Lin, S.; Ma, Z.; Huang, Y.; Sun, Y.; Yi, H. Chronic Obstructive Pulmonary Disease Is Characterized by Reduced Levels and Defective Suppressive Function of Regulatory B Cells in Peripheral Blood. Mol. Immunol. 2022, 141, 87–93.

85. Bosisio, D.; Ronca, R.; Salvi, V.; Presta, M.; Sozzani, S. Dendritic Cells in Inflammatory Angiogenesis and Lymphangiogenesis. Curr. Opin. Immunol. 2018, 53, 180–186.

86. Givi, M.E.; Redegeld, F.A.; Folkerts, G.; Mortaz, E. Dendritic Cells in Pathogenesis of Copd. Curr. Pharm. Des. 2012, 18, 2329–2335.

87. Paplinska-Goryca, M.; Misiukiewicz-Stepien, P.; Proboszcz, M.; Nejman-Gryz, P.; Gorska, K.; Krenke, R. The Expressions of Tslp, Il-33, and Il-17a in Monocyte Derived Dendritic Cells from Asthma and Copd Patients Are Related to Epithelial-Macrophage Interactions. Cells 2020, 9, 1944.

88. Kitajima, M.; Lee, H.C.; Nakayama, T.; Ziegler, S.F. Tslp Enhances the Function of Helper Type 2 Cells. Eur. J. Immunol. 2011, 41, 1862–1871.

89. Elder, M.J.; Webster, S.J.; Fitzmaurice, T.J.; Shaunak, A.S.D.; Steinmetz, M.; Chee, R.; Mallat, Z.; Cohen, E.S.; Williams, D.L.; Gaston, J.S.H.; et al. Dendritic Cell-Derived Tslp Negatively Regulates Hif-1alpha and Il-1beta During Dectin-1 Signaling. Front. Immunol. 2019, 10, 921.

90. Su, Z.; Lin, J.; Lu, F.; Zhang, X.; Zhang, L.; Gandhi, N.B.; de Paiva, C.S.; Pflugfelder, S.C.; Li, D.Q. Potential Autocrine Regulation of Interleukin-33/St2 Signaling of Dendritic Cells in Allergic Inflammation. Mucosal Immunol. 2013, 6, 921–930.

91. Paplinska-Goryca, M.; Misiukiewicz-Stepien, P.; Proboszcz, M.; Nejman-Gryz, P.; Gorska, K.; Zajusz-Zubek, E.; Krenke, R. Interactions of Nasal Epithelium with Macrophages and Dendritic Cells Variously Alter Urban Pm-Induced Inflammation in Healthy, Asthma and Copd. Sci. Rep. 2021, 11, 13259.

92. Van Pottelberge, G.R.; Bracke, K.R.; Demedts, I.K.; de Rijck, K.; Reinartz, S.M.; van Drunen, C.M.; Verleden, G.M.; Vermassen, F.E.; Joos, G.F.; Brusselle, G.G. Selective Accumulation of Langerhans-Type Dendritic Cells in Small Airways of Patients with Copd. Respir. Res. 2010, 11, 35.

93. Freeman, C.M.; Martinez, F.J.; Han, M.K.; Ames, T.M.; Chensue, S.W.; Todt, J.C.; Arenberg, D.A.; Meldrum, C.A.; Getty, C.; McCloskey, L.; et al. Lung Dendritic Cell Expression of Maturation Molecules Increases with Worsening Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2009, 180, 1179–1188.

94. Vassallo, R.; Walters, P.R.; Lamont, J.; Kottom, T.J.; Yi, E.S.; Limper, A.H. Cigarette Smoke Promotes Dendritic Cell Accumulation in Copd; A Lung Tissue Research Consortium Study. Respir. Res. 2010, 11, 45.

95. Janela, B.; Patel, A.A.; Lau, M.C.; Goh, C.C.; Msallam, R.; Kong, W.T.; Fehlings, M.; Hubert, S.; Lum, J.; Simoni, Y.; et al. A Subset of Type I Conventional Dendritic Cells Controls Cutaneous Bacterial Infections through Vegfalpha-Mediated Recruitment of Neutrophils. Immunity 2019, 50, 1069–1083.e8.

96. Quatrini, L.; della Chiesa, M.; Sivori, S.; Mingari, M.C.; Pende, D.; Moretta, L. Human Nk Cells, Their Receptors and Function. Eur. J. Immunol. 2021, 51, 1566–1579.

97. Cong, J.; Wei, H. Natural Killer Cells in the Lungs. Front. Immunol. 2019, 10, 1416.

98. Hervier, B.; Russick, J.; Cremer, I.; Vieillard, V. Nk Cells in the Human Lungs. Front. Immunol. 2019, 10, 1263.
99. Rao, Y.; Le, Y.; Xiong, J.; Pei, Y.; Sun, Y. Nk Cells in the Pathogenesis of Chronic Obstructive Pulmonary Disease. Front. Immunol. 2021, 12, 666045.
100. Marquardt, N.; Kekalainen, E.; Chen, P.; Kvedaraite, E.; Wilson, J.N.; Ivarsson, M.A.; Mjosberg, J.; Berglin, L.; Safholm, J.; Manson, M.L.; et al. Human Lung Natural Killer Cells Are Predominantly Comprised of Highly Differentiated Hypofunctional Cd69(-)Cd56(Dim) Cells. J. Allergy Clin. Immunol. 2017, 139, 1321–1330.e4.
101. Radomska-Lesniewska, D.M.; Bialoszewska, A.; Kaminski, P. Angiogenic Properties of Nk Cells in Cancer and Other Angiogenesis-Dependent Diseases. Cells 2021, 10, 1621.