The Role of Innate and Adaptive Immune Cells in the Immunopathogenesis of Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a chronic and progressive inflammatory disease of the airways and lungs that results in limitations of continuous airflow and is caused by exposure to noxious gasses and particles. A major cause of morbidity and mortality in adults, COPD is a complex disease pathologically mediated by many inflammatory pathways. Macrophages, neutrophils, dendritic cells, and CD8+ T-lymphocytes are the key inflammatory cells involved in COPD. Recently, the non-coding small RNA, micro-RNA, have also been intensively investigated and evidence suggest that it plays a role in the pathogenesis of COPD. Here, we discuss the accumulated evidence that has since revealed the role of each inflammatory cell and their involvement in the immunopathogenesis of COPD. Mechanisms of steroid resistance in COPD will also be briefly discussed.

Keywords: Pulmonary Disease, Chronic Obstructive; Macrophages; Neutrophils; Dendritic Cells; Lymphocytes

Introduction

In 2020, chronic obstructive pulmonary disease (COPD) will be the third leading cause of death worldwide (from sixth in 1990) and fifth leading cause of years lost through early mortality or handicap (disability-adjusted life years) from previously 12th in 1990. However, recent studies suggest COPD is already the third most common cause of death, worldwide.

For the population without COPD over the age of 40, the risk of developing COPD within the next 40 years was 12.7% for men and 8.3% for women. In patients with very severe COPD, 26% died after 1 year of follow-up, whereas 2.8% died among the non-COPD subjects.

COPD, a common and preventable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gasses. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines airflow obstruction as spirometry where the ratio of forced expiratory volume in the first second to forced vital capacity after bronchodilatation is less than 0.70.

Cigarette Smoke Exposure as a Model to Study COPD

Cigarette smoking (CS) is an established risk factor for COPD, and study suggests that CS exposure could have a suppressive effect on host innate immunity including structural and functional changes in the respiratory ciliary epithelium, and immune cells such as alveolar macrophages (AMs), neutrophils, and lymphocytes. Moreover, CS could
also cause defect in the generation of adaptive immunity in the lung. CS exposure is the most appropriate model to study the pathogenesis of emphysema in mice. Following cigarette exposure for 26, 52, and 65 weeks, structural changes were observed and accompanied by altered lung function at 26 and 52 weeks. After 13 weeks of CS exposure-free period, most biochemical, histopathological, and morphometrical alterations were restored, while emphysema was observed to persist in 18% of mice exposed to CS at 65 weeks. These findings suggest that the cigarette exposure induced emphysematous changes in the lungs, accompanied by altered lung function and inflammatory cell infiltration. There are data demonstrating that smoking is associated with up- or down-regulation of many genes in the airway epithelium and, interestingly, ex-smokers continue to have persistent up- or down-regulation of many genes, despite smoking cessation.

**Early Changes in Airway Epithelium in the Pathogenesis of COPD**

Most of the normal human airway is lined by a pseudostratified epithelium of ciliated cells, secretory cells and 6%–30% basal cells (BCs). In COPD, the remodeling of the airway epithelium, such as squamous metaplasia and mucous hyperplasia that occur during injury, may considerably disturb the innate immune functions of the airway epithelium. Although inflammatory reaction by immune processes plays a significant role in the pathogenesis of COPD, the earliest abnormalities in the COPD lung caused by smoking are hyperplasia of airway BC, the stem/progenitor cells of the ciliated and secretory cells that are central to pulmonary host defense. Apart from BC hyperplasia, smoking induces a number of COPD-relevant airway epithelial remodeling phenotypes that are likely initiated in the BC population, including mucous cell hyperplasia, squamous cell metaplasia, epithelial-mesenchymal transition, altered ciliated and non-mucous secretory cell differentiation, and suppression of junctional barrier integrity.

**Inflammatory Cells in COPD**

A smoking-induced inflammatory reactions in the airways and lung parenchyma have long been accepted to be the major cause of COPD in smokers. Cigarette smoke activates innate immune cells by triggering pattern recognition receptors to release ‘danger signal’ that act as ligands to Toll-like receptors, triggering the production of cytokines and inducing innate inflammation. Impaired immune function contributes to the development of COPD and disease progression is further exacerbated by infections due to impaired immune responses. Severity and course of acute exacerbations of COPD reflects the capacity of the adaptive immune system in modulating the innate response to pathogen (‘the Goldilocks hypothesis’). Basically, this hypothesis states that there is no such thing as bad inflammation; it all depends on how and when. Goldilocks hypothesis is the state when the innate and adaptive immune response successfully eliminates the infection, and the response is mild and transient, not too much and not too little. The immune inflammatory changes associated with COPD are linked to a tissue-repair and remodeling process that increases mucus production and causes emphysematous destruction of the gas-exchanging surface of the lung.

| Table 1. The role of innate and adaptive immune cells in the pathogenesis of COPD |
|---------------------------------|-------------------------------------------------|--------------------------------------------------|
| **Cell**                       | **Role and characteristic**                      | **Specific therapeutic intervention**             |
| Macrophage                     | Secretion of chemotactic factors                 | Simvastatin                                      |
|                                | Impaired ability to clear respiratory pathogens and apoptotic cells |                                                  |
| Dendritic cell                 | Increased amount of pulmonary immature dendritic cells | Resveratrol                                      |
|                                | Induce adaptive immune responses encompassing T helper CD4+ T cells, CD8+ cytotoxicity, and B-cell responses |                                                  |
| Neutrophil                     | Increased survival and motility, but lack direction | Sivelestat (NE inhibitor)                         |
|                                | Secreted NE, Cat-G, PR3, MMPs                    | RWJ-355871 (Cat-G inhibitor)                     |
|                                |                                                  | A1AT (PR3 inhibitor)                             |
|                                |                                                  | AZD1236 (MMP-9 and MMP-12 inhibitor)             |
| Lymphocyte CD8+                | Associated with decline of lung function in COPD patients | CD137 inhibition                                |
|                                | Secret cytotoxic perforins and granzyme B which cause cell death and apoptosis |                                                  |
|                                | Express reduced glucocorticoid receptor           |                                                  |
| Lymphocyte CD4+                | Mediate autoimmune response in COPD             |                                                  |
|                                | Facilitate B-cell production of IgG autoantibodies in COPD patients |                                                  |

COPD: chronic obstructive pulmonary disease; NE: neutrophil elastase; Cat-G: cathepsin G; PR3: proteinase 3; MMP: matrix metalloproteinase; A1AT: antiprotease α1-antitrypsin.
The inflamed airways of COPD patients contain several inflammatory cells including neutrophils, macrophages, T lymphocytes, and dendritic cells (DCs)\(^{23}\) (Table 1). Recent evidence also found increased population of goblet cells in COPD patient\(^{24}\), which cause the mucous overproduction and hypersecretion\(^{25}\). It seems likely that, only when all inflammatory cell types (i.e., CD4+, CD68, neutrophils, and macrophages) are present in the lung, the airways remodeling and parenchymal destruction characteristic of COPD will ensue\(^{27}\). These cells release the reactive oxygen species, chemokines (e.g., interleukin [IL]-8), cytokines (e.g., tumor necrosis factor alpha [TNF-\(\alpha\)]) and proteases (e.g., neutrophil elastase [NE] and matrix metalloproteinase [MMP]) that are instrumental in producing a chronic inflammatory state\(^{28}\). In the following sections, we will discuss each inflammatory cell that participates in the immunopathogenesis of COPD.

**Macrophage**

AMs have been identified as one of the major cell types that plays a key role in orchestrating the inflammatory events associated with the pathophysiology of COPD\(^{29}\). The number of AM is markedly increased in the lungs of patients with COPD as a result of increased recruitment, proliferation and survival\(^{30}\). One of the major functions of macrophages is the secretion of chemotactic factors and this function is markedly increased on exposure to CS\(^{31}\). However, it is also found that macrophage in COPD has impaired ability to clear respiratory pathogens and apoptotic cells\(^{32}\). The reduced phagocytic ability of macrophage may drive the persistence of inflammation in COPD\(^{33}\).

Genome-wide analysis has underscored the heterogeneity and plasticity of macrophage phenotype which lead to the introduction of the term M1 (classical activation) and M2 (alternative activation)\(^{34}\). M1 phenotype macrophages express various pro-inflammatory mediators including TNF-\(\alpha\), IL-1, IL-6, reactive nitrogen and oxygen intermediates, which have a strong microbicidal and tumoricidal activity; while M2 phenotype is involved in tissue remodeling and characterized with anti-inflammatory properties\(^{35}\). It is said that the surrounding pulmonary environment in COPD may generate a specific phenotype that is permanently pro-inflammatory (M1)\(^{36}\). Among COPD patients, M2 macrophages were reduced in current smokers compared to ex-smokers which indicate that smoking cessation in COPD is associated with macrophage polarization towards an anti-inflammatory phenotype\(^{37}\). However another study suggests, rather than up-regulating the M1 polarization program as expected, CS induces in AM of COPD smokers the opposite phenotype, characterized by a substantial down-regulation of the M1-related genes\(^{38}\). Obviously, these conflicting results indicate that smoking induced a complex suppression of immune response in the lung, including deactivation of AM inflammatory and host defense function, and development of tissue remodeling.

The source of macrophage activation is still under intense investigation. Macrophage could be induced by TNF-\(\alpha\)\(^{39}\) and IL-8\(^{40}\). In one study by Bozinovski et al\(^{41}\), activation of innate cellular sources of IL-17A is an essential mediator of macrophage accumulation in CS-exposed lungs. Targeting non-conventional T cell sources of IL-17A may offer an alternative strategy to reduce pathogenic macrophages in COPD. However, it has also been found that IL-17A contributes to normal lung homeostasis and does not mediate CS-induced loss of lung structure and pulmonary function\(^{42}\).

‘Macrophage-targeted therapy’ has been studied in many centers. It has been reported that simvastatin, member of statin which has immunomodulatory properties, reversed the IL-17A/IL-10 imbalance in the airways and reduced sputum macrophage but not neutrophil counts in patients with COPD\(^{43}\). Generally, simvastatin could provide substantial benefits in patients with COPD due to (1) reduction of cytokine secretion (TNF-\(\alpha\), IL-6, and IL-8) and neutrophil infiltration into the lung; (2) attenuation of the fibrotic activity in the lung leading to small airways fibrosis and irreversible airflow limitation; (3) antioxidant and anti-inflammatory effects on skeletal muscle; (4) reduced inflammatory response to pulmonary infection; and (5) inhibition of the epithelial-mesenchymal transition, a precursor event to lung cancer\(^{44}\). In one in vivo study, pretreatment with simvastatin prior to and continued throughout smoke exposure reduced the influx of macrophages into the lung and airways\(^{45}\). Molecular mechanism of simvastatin in attenuating CS-induced emphysema-like abnormality in COPD has been described by Kim et al\(^{46}\). In their in vitro study, simvastatin reversed CS-induced MMP-9 expressions in AM. However, there are clinical trials that suggest simvastatin did not affect exacerbation rates or the time to a first exacerbation\(^{47}\), and did not reduce circulating inflammatory markers in patients with COPD\(^{48}\). Controversies about the use of statin in COPD still remain. Recently, positive result came from study conducted by Ingebrigtsen et al\(^{49,50}\), who found that statin was associated with reduced odds of exacerbations in COPD patient, in particular those who have coexisting cardiovascular disease. This finding was consistent with other study, involving 1,584 patients, that confirm the efficacy of statin in the reduction of COPD exacerbation\(^{51}\).

**Dendritic Cells**

DCs in the lung have an essential role in defense mechanism based on their anatomical location that creates a functional cellular interface between the external environment and the internal lung microenvironment\(^{52}\). DCs are in charge of capturing antigens in peripheral tissues, transporting them

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Neutrophil

Neutrophils are also aberrant with increased survival and motility, but lack of direction could lead to more widespread destruction of host matrix during migration. Neutrophil secretion of NE and the proteolytic activity of NE not only destroys pathogens but also degrades host matrix tissues by generating a localized protease-antiprotease imbalance in COPD. Although NE was identified as a therapeutic target for COPD more than 30 years ago, only Sivelestat (ONO-5046), an NE inhibitor from Ono Pharmaceutical, has been approved for clinical use in Japan, but not in United States.

There are two similar neutrophil serine proteases that coexist with NE in COPD: cathepsin G (Cat-G); and proteinase 3 (PR3). Cat-G is a neutral proteinase originating from human neutrophils that displays a unique dual specificity (trypsin- and chymotrypsin-like); thus, its enzymatic activity is difficult to control. Anti-inflammatory pharmacology of RWJ-355871, an inhibitor of Cat-G, has been tested in animal models of inflammation that represent COPD, and showed promising result in terms of reduction of smoke-induced neutrophilia. Meanwhile, PR3 is a multifunctional serine proteinase mainly located in the azurophilic granules and on the cell surface of neutrophils and able to degrade many critical components of the extracellular matrix, including elastin, type IV collagen, fibronectin, and laminin. In one report, PR3 is inhibited by the antiprotease α1-antitrypsin (A1AT).

MMPs have an NH2 terminal pro-domain, an active site zinc atom, and a COOH terminal hemopexin domain that regulates the binding of the enzymes to their substrates. In cigarette smoke-induced animal models of emphysema, MMP-12 appears to play a consistent and important role, whereas the data for other MMPs are controversial. Other studies suggest MMP-9 is associated with acute exacerbations of COPD, and airway remodeling. A phase IIA study has been conducted to evaluate the effects of AZD1236, a selective MMP-9 and MMP-12 inhibitor, in modifying differential cell count and in reducing TNF-α level in induced sputum. Although AZD1236 was generally well tolerated over 6 weeks in patients with moderate-to-severe COPD, no clinical efficacy of AZD1236 was demonstrated in the study.

Recently, Taylan et al. reported that neutrophil-lymphocyte ratio (NLR) was altered in patients with COPD and could be used for identifying the severity of inflammation and recognition of acute exacerbation, similar to C-reactive protein and erythrocyte sedimentation rate. For an NLR cutoff of 3.29, sensitivity for detecting exacerbation of COPD was 80.8% and specificity was 77.7%. Moreover, NLR values of the stable COPD patients were significantly higher than those of the healthy controls (p<0.001).

Lymphocyte CD8+

Decline in lung function in COPD patients has been correlated to the number of CD8+ T cells present in the lung as well as to a decline in the ratio of CD4+/CD8+ T cells. Regardless of smoking habits, CD8+ T-cell activation was found in COPD, supporting the concept that this T-cell subset may play a role in the pathogenesis of COPD. Smokers with COPD had a decreased ratio CD4+/CD8+ in the paratracheal lymph node compared to smokers without COPD. Moreover, CD8+ T cells were found in both bronchial epithelium and airway lumen of COPD patients. Lung CD8+ T cells might contribute to progression of COPD indirectly via IFN-γ production or directly via cytosis, and in one in vitro study, stimulation of lung CD8+ T cells with IL-18 plus IL-12 markedly increased production of IFN-γ and TNF-α, whereas IL-15 stimulation induced increased intracellular perforin expression. Cytotoxic perforins and granzyme B, produced by CD8+ T cells, can cause cell death and apoptosis which are feature of emphysema pathology. Other CD8+ T-cell product, IFN-inducible protein-10, induces production of macrophage elastase (MMP-12) that degrades elastin, both causing lung destruction directly and generating elastin fragments that serve as monocyte chemokines augmenting macrophage-mediated lung destruction. In vitro CD8+ cells were increased in both current- and ex-smoker COPD groups; under CS exposure, these cells expressed significantly more interferon IFN-γ, granzyme, and perforin compared with CS-exposed CD8+/CD28− cells. Moreover, CD8+/CD28− cells have...
reduced glucocorticoid receptor which contributes to steroid resistance in COPD\textsuperscript{89}. Recent evidence suggest that targeting CD137 expression in CD8+/CD28– lymphocyte T cells was associated with down-regulation of IFN-\(\gamma\), TNF-\(\alpha\), and granzyme B\textsuperscript{90}.

**Lymphocyte CD4+**

CD4+ T cells are important in amplifying inflammatory responses by other immune effector cells by means of promoting the long-term survival of CD8+ T cells and activating antibody-elaborating B cells\textsuperscript{81}. Autoimmune responses mediated by CD4+ T cells may contribute to the development of COPD\textsuperscript{52}. CD4+ T cells might facilitate B cell production of IgG autoantibodies in COPD patients, because ~70% of COPD patients had circulating IgG autoantibodies against epithelial cells compared to 10% among non-smoking controls and 13% of non-COPD cigarette smokers\textsuperscript{83}. Increased CD4+/CD28– T cells in COPD indicates that chronic antigen exposure, e.g., through contents of smoke, leads to loss of CD28 and up-regulation of natural killer cell receptors expression on T cells in susceptible patients\textsuperscript{84}.

**MicroRNA in COPD**

MicroRNAs (miRNAs) are small non-coding RNA molecules that negatively regulate gene expression at the post-transcriptional level\textsuperscript{85,86}. Altered miRNA expression profiles may be associated with pathological processes within the lung and lead to the development of various pulmonary diseases, including inflammatory lung diseases\textsuperscript{87}.

Among well studied miRNA, miR-15b, miR-223, and miR-1274a were the most important miRNAs in patients with COPD\textsuperscript{88} to both emphysematous and fibrotic areas and was differentially expressed according to the GOLD classification of COPD. miR-15b was increased in COPD samples compared with smokers without obstruction and localized to both emphysematous and fibrotic areas and was differentially expressed according to the GOLD classification of COPD. Meanwhile, miR-223 and miR-1274a were the most affected miRNAs in subjects with COPD compared with smokers without obstruction, miRNA-34c is associated with emphysema severity\textsuperscript{89}. Healthy subject showed higher expression of let-7c and miR-125b compared with COPD subject\textsuperscript{92}. Target gene of let-7c is tumor necrotizing factor receptor II (TNFR-II), and the study confirmed that the concentration of TNFR-II was inversely correlated with the sputum levels of let-7c.

**Mechanism of Steroid Resistance in COPD**

Resistance to the anti-inflammatory effects of corticosteroids is common in COPD\textsuperscript{93}. Regular treatment with high doses of inhaled glucocorticoids does not significantly change the number of inflammatory cells in bronchial biopsies from patients with moderate COPD\textsuperscript{94}. Several molecular mechanisms of glucocorticoid resistance have now been identified, including activation of mitogen-activated protein kinase pathways by certain cytokines, excessive activation of the transcription factor activator protein 1, reduced histone deacetylase-2 (HDAC2) expression, raised macrophage migration inhibitory factor, and increased P-glycoprotein–mediated drug efflux\textsuperscript{95}. One of the novel strategies for overcoming steroid resistance is to increase HDAC2 expression by theophylline or phosphoinositide 3-kinase \(\delta\) inhibitors\textsuperscript{96}.

Several studies indicate that increased expression of IFN-\(\gamma\) has been correlated with macrophage-mediated steroid-resistant phenotype in chronic inflammatory disease\textsuperscript{97,98}. IFN-\(\gamma\) is a cytokine produced by Th1 cell and may play an important role in inflammation in individuals with COPD\textsuperscript{82}. It has been demonstrated that COPD patients have increased level of IFN-\(\gamma\) signaling in their lung\textsuperscript{86}. Moreover, it has been shown that inhibition of IFN-\(\gamma\) signaling is a potentially novel strategy to sensitize macrophage to steroid in COPD\textsuperscript{99}. Despite these findings, conflicting evidence also suggest that IFN-\(\gamma\) reversed steroid resistant in COPD through the restoration of dexamethasone-induced glucocorticoids-receptor \(\alpha\) nuclear translocation in T cell\textsuperscript{87}. Taken together, targeting IFN-\(\gamma\) as a mean to sensitize COPD patients to steroid need further investigations because of the wide variation of immune cells response to IFN-\(\gamma\)-targeted approach.

Lymphocyte has also been associated with steroid-resistant in COPD. One report suggests that T lymphocytes from the airways COPD patients display corticosteroid insensitivity via increased IFN-\(\gamma\) production\textsuperscript{88}. Another work found that there is subset of lymphocyte population, CD8+/CD28– lymphocyte cells, that is resistant to steroid and this subset of population was increased in COPD\textsuperscript{93}. Other mechanisms of lymphocyte-associated steroid resistance in COPD are reduced population of Treg cells (through reduced expression of IL-19 and vitamin D\textsubscript{3}) and increased population of IL17-producing Th17\textsuperscript{94}.

**Conclusion**

COPD is a complex inflammatory disease of lung and exposure to CS is the most appropriate model to study the pathophysiology of COPD. The abnormalities in the earliest phase of smoking COPD are hyperplasia of airway BCs, the stem/progenitor cells of the ciliated and secretory cells that are central to pulmonary host defense. The airways of COPD patients
have inflammatory cells including neutrophils, macrophages, T lymphocytes, and DC. Despite the inflammation characteristic of COPD, treatment with steroid does not significantly change the number of inflammatory cells due to several resistance mechanisms. Further studies are required to verify the effect of biological intervention on the inflammatory cells and find the ways to overcome the steroid resistance in COPD.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev 2009;18:213-21.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.
3. Afonso AS, Verhamme KM, Sturkenboom MC, Brusselle GG. COPD in the general population: prevalence, incidence and survival. Respir Med 2011;105:1872-84.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease; 2014.
5. Bellinger CR, Peters SP. Outpatient chronic obstructive pulmonary disease management: going for the GOLD. J Allergy Clin Immunol Pract 2015;3:471-8.
6. Salvi S. Tobacco smoking and environmental risk factors for chronic obstructive pulmonary disease. Clin Chest Med 2014;35:17-27.
7. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.
8. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. Inflamm Res 2008;57:497-503.
9. Lugade AA, Bogner PN, Thatcher TH, Sime PJ, Phripps RP, Thanavala Y. Cigarette smoke exposure exacerbates lung inflammation and compromises immunity to bacterial infection. J Immunol 2014;192:5226-35.
10. Rinaldi M, Maes K, De Vleeschauwer S, Thomas D, Verbeke EK, Decramer M, et al. Long-term nose-only cigarette smoke exposure induces emphysema and mild skeletal muscle dysfunction in mice. Dis Model Mech 2012;5:333-41.
11. Tsujii H, Fujimoto H, Lee KM, Renne R, Iwanaga A, Okubo C, et al. Characterization of biochemical, functional and structural changes in mice respiratory organs chronically exposed to cigarette smoke. Inhal Toxicol 2015;27:342-53.
12. Wang G, Wang R, Strulovici-Barclay Y, Salit J, Staudt MR, Ahmed J, et al. Persistence of smoking-induced dysregulation of miRNA expression in the small airway epithelium despite smoking cessation. PLoS One 2015;10:e0120824.
13. Rock JR, Randell SH, Hogan BL. Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodeling. Dis Model Mech 2010;3:545-56.
14. Puchelle E, Zahm JM, Tournier JM, Coraux C. Airway epithelial repair, regeneration, and remodeling after injury in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2006;3:726-33.
15. Crystal RG. Airway basal cells. The “smoking gun” of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;190:1355-62.
16. Shaykhiev R, Crystal RG. Early events in the pathogenesis of chronic obstructive pulmonary disease: smoking-induced reprogramming of airway epithelial basal progenitor cells. Am Am Thorac Soc 2014;11 Suppl 5:S252-8.
17. Cosío MG, Majo J, Cosío MG. Inflammation of the airways and lung parenchyma in COPD: role of T cells. Chest 2002;121(5 Suppl):160S-5S.
18. Rovina N, Koutsoukou A, Koulouris NG. Inflammation and immune response in COPD: where do we stand? Mediators Inflamm 2013;2013:413735.
19. Keller IE, Vosykia O, Takenaka S, Kloss A, Dahlmann B, Willems LJ, et al. Regulation of immunoproteasome function in the lung. Sci Rep 2015;5:10230.
20. Curtis JL, Freeman CM, Hogg JC. The immunopathogenesis of chronic obstructive pulmonary disease: insights from recent research. Proc Am Thorac Soc 2007;4:512-21.
21. Soriano JB, Agusti A. The yin and yang of COPD: or balancing repair (yang) and inflammation (yin). Eur Respir J 2008;32:1426-7.
22. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. Annu Rev Pathol 2009;4:435-59.
23. Givi ME, Peck MJ, Boon L, Mortaz E. The role of dendritic cells in the pathogenesis of cigarette smoke-induced emphysema in mice. Eur J Pharmacol 2013;721:259-66.
24. Kim V, Oros M, Durra H, Kelsen S, Aksoy M, Cornwell WD, et al. Chronic bronchitis and current smoking are associated with more goblet cells in moderate to severe COPD and smokers without airflow obstruction. PLoS One 2015;10:e0116108.
25. Ramos FL, Krahnke JS, Kim V. Clinical issues of mucus accumulation in COPD. Int J Chron Obstruct Pulmon Dis 2014;9:139-50.
26. Celli BR. Predictors of mortality in COPD. Respir Med 2010;104:773-9.
27. Murugan V, Peck MJ. Signal transduction pathways linking the activation of alveolar macrophages with the recruitment of neutrophils to lungs in chronic obstructive pulmonary disease. Exp Lung Res 2009;35:439-85.

28. Barnes PJ. Alveolar macrophages in chronic obstructive pulmonary disease (COPD). Cell Mol Biol (Noisy-le-grand) 2004;50 Online Pub:OL627-37.

29. Hiemstra PS. Altered macrophage function in chronic obstructive pulmonary disease. Ann Am Thorac Soc 2013;10 SupplS180-5.

30. Holloway RA, Donnelly LE. Immunopathogenesis of chronic obstructive pulmonary disease. Curr Opin Pulm Med 2013;19:95-102.

31. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. Immunol 2010;32:593-604.

32. Liu YC, Zou XB, Chai YF, Yao YM. Macrophage polarization in inflammatory diseases. Int J Biol Sci 2014;10:5320-9.

33. Kunz LJ, Lapperre TS, Snoeck-Stroband JB, Budulac SE, Tiemens W, van Wijngaarden S, et al. Smoking status and anti-inflammatory macrophages in bronchoalveolar lavage and induced sputum in COPD. Respir Res 2011;12:34.

34. Shakhiev R, Krause A, Salit J, Strulovici-Barel Y, Harvey BG, O’Connor TP, et al. Smoking-dependent reprogramming of alveolar macrophage polarization: implication for pathogenesis of chronic obstructive pulmonary disease. J Immunol 2009;183:2867-83.

35. Churg A, Wang RD, Tai H, Wang X, Xie C, Dai J, et al. Macrophage metalloelastase mediates acute cigarette smoke-induced inflammation via tumor necrosis factor-alpha release. Am J Respir Crit Care Med 2003;167:1083-9.

36. Culpitt SV, Rogers DF, Shah P, De Matos C, Russell RE, Donnelly LE, et al. Impaired inhibition by dexamethasone of cytokine release by alveolar macrophages from patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:24-31.

37. Bozinovski S, Seow HJ, Chan SP, Anthony D, McQualter J, Hansen V, et al. Innate cellular sources of interleukin-17A regulate macrophage accumulation in cigarette-smoke-induced lung inflammation in mice. Clin Sci (Lond) 2015;129:785-96.

38. Voss M, Wolf L, Kamyschnikov A, Wonnennenberg B, Honcke A, Herr C, et al. IL-17A contributes to maintenance of pulmonary homeostasis in a murine model of cigarette smoke-induced emphysema. Am J Physiol Lung Cell Mol Physiol 2015;309:L188-95.

39. Maneesechoteuwan K, Wongkajornsilp A, Adcock IM, Barnes PJ. Simvastatin suppresses airway IL-17 and upregulates IL-10 in patients with stable COPD. Chest 2015;148:1164-76.

40. Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. Eur Respir Rev 2009;18:222-32.

41. Davis BB, Zeki AA, Bratt JM, Wang L, Filosto S, Walby WE, et al. Simvastatin inhibits smoke-induced airway epithelial injury: implications for COPD therapy. Eur Respir J 2013;42:350-61.

42. Kim SE, Thanh Thuy TT, Lee JH, Ro JY, Bae YA, Kong Y, et al. Simvastatin inhibits induction of matrix metalloproteinase-9 in rat alveolar macrophages exposed to cigarette smoke extract. Exp Mol Med 2009;41:277-87.

43. Criner GJ, Connnett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. N Engl J Med 2014;370:2201-10.

44. Kaczmarek P, Sladek K, Skucha W, Rzeszutko M, Iwaniec T, Dziedzina S, et al. The influence of simvastatin on selected inflammatory markers in patients with chronic obstructive pulmonary disease. Pol Arch Med Wewn 2010;120:11-7.

45. Ingebrigtsen TS, Marott JL, Nordestgaard BG, Lange P, HALLAS J, Vestbo J. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. Thorax 2015;70:33-40.

46. Ingebrigtsen T, Marott J, Nordestgaard B, Lange P, HALLAS J, Vestbo J. Statin use and risk of exacerbations in individuals with COPD: the Copenhagen general population study. Eur Respir J 2014;44(Suppl 58):i26.

47. Wang MT, Lo YW, Tsai CL, Chang LC, Malone DC, Chu CL, et al. Statin use and risk of COPD exacerbation requiring hospitalization. Am J Med 2013;126:604-10.

48. Condon TV, Sawyer RT, Fenton MJ, Riches DW. Lung dendritic cells at the innate-adaptive immune interface. J Leukoc Biol 2011;90:883-95.

49. Chabaud M, Heuze ML, Bretou M, Vargas P, Maiuri P, Solanes P, et al. Cell migration and antigen capture are antagonistic processes coupled by myosin II in dendritic cells. Nat Commun 2015;6:7526.

50. Van Pottelberge GR, Bracke KR, Joos GF, Brusselle GG. The role of dendritic cells in the pathogenesis of COPD: liaison officers in the front line. COPD 2009;6:284-90.

51. Vassallo R, Walters PR, Lamont J, Kottom TJ, Yi ES, Limper AH. Cigarette smoke promotes dendritic cell accumulation in COPD: a Lung Tissue Research Consortium study. Respir Res 2010;11:45.

52. Givi ME, Redegeld FA, Folters G, Mortaz E. Dendritic cells in pathogenesis of COPD: liaison officers in the front line. COPD 2009;6:284-90.

53. Tsoumakidou M, Bouloukaki I, Koutala H, Kouvidi K, Mitroussa I, Zakynthinos S, et al. Decreased sputum mature dendritic cells in healthy smokers and patients with chronic obstructive pulmonary disease. Int Arch Allergy Immunol 2009;150:389-97.

54. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011;378:1015-26.

55. Wang X, Zhang C, Huang G, Han D, Guo Y, Meng X, et al. Resveratrol inhibits dysfunction of dendritic cells from chronic obstructive pulmonary disease patients through...
promoting miR-34. Int J Clin Exp Pathol 2015;8:5145-52.
56. Silva AM, Oliveira MI, Sette L, Almeida CR, Oliveira MJ, Barbosa MA, et al. Resveratrol as a natural anti-tumor necrosis factor-alpha molecule: implications to dendritic cells and their cross-talk with mesenchymal stromal cells. PLoS One 2014;9:e91406.
57. Tsai YE, Hwang TL. Neutrophil elastase inhibitors: a patent review and potential applications for inflammatory lung diseases (2010-2014). Expert Opin Ther Pat 2015;25:1145-58.
58. Lucas SD, Costa E, Guedes RC, Moreira R. Targeting COPD: advances on low-molecular-weight inhibitors of human neutrophil elastase. Med Res Rev 2013:33 Suppl 1:E73-101.
59. Guyot N, Wartelle J, Malleret L, Todorov AA, Devouassoux G, Pacheco Y, et al. Unopposed cathepsin G, neutrophil elastase, and proteinase 3 cause severe lung damage and emphysema. Am J Pathol 2014;184:2197-210.
60. Kosikowska P, Lesner A. Inhibitors of cathepsin G: a patent review (2005 to present). Expert Opin Ther Pat 2013:23:1611-24.
61. Maryanoff BE, de Garavilla L, Greco MN, Haertlein BJ, Wells GI, Andrade-Gordon P, et al. Dual inhibition of cathepsin G and chymase is effective in animal models of pulmonary inflammation. Am J Respir Crit Care Med 2010;181:247-53.
62. Sinden NJ, Stockley RA. Proteinase 3 activity in sputum from subjects with alpha-1-antitrypsin deficiency and COPD. Eur Respir J 2013;41:1042-50.
63. Rooney CP, Taggart C, Coakley R, McElvaney NG, O’Neill SJ. Anti-proteinase 3 antibody activation of neutrophils can be increased with chronic obstructive pulmonary disease severity and with in vitro stimulation by IL-18 or IL-15. J Immunol 2010;184:6650-13.
64. Tetley TD. Inflammatory cells and chronic obstructive pulmonary disease. Curr Drug Targets Inflamm Allergy 2005;4:607-18.
65. Hodge G, Houghton AM, Quintero PA, Grumelli S, Owen CA, Shapiro SD. CD8+ T cells are required for inflammation/cytotoxic lymphocytes. Respir Res 2015;16:2.
66. Papakonstantinou E, Karakulakis G, Batziou S, Savic S, Roth M, Tamm M, et al. Acute exacerbations of COPD are associated with significant activation of matrix metalloproteinase 9 irrespectively of airway obstruction, emphysema and infection. Respir Res 2015;16:78.
67. Churg A, Zhou S, Wright JL. Series "matrix metalloproteinases in lung health and disease": matrix metalloproteinases in COPD. Eur Respir J 2012;39:2197-209.
68. Dahl R, Tillestad I, Lindqvist A, Wielders P, Wray H, Wang M, et al. Effects of an oral MMP-9 and -12 inhibitor, AZD1236, on biomarkers in moderate/severe COPD: a randomised controlled trial. Pulm Pharmacol Ther 2012;25:169-77.
69. Taylan M, Demir M, Kaya H, Selimoglu Sen H, Abakay O, Carkanat AI, et al. Alterations of the neutrophil-lymphocyte ratio during the period of stable and acute exacerbation of chronic obstructive pulmonary disease patients. Clin Respir J 2015 Jun 19 [Epub]. http://dx.doi.org/10.1111/crj.12336.
70. Gunay E, Sarinc Ulasi S, Akar O, Ahsen A, Gunay S, Koyuncu T, et al. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014;37:374-80.
71. Glader P, von Wachenfeldt K, Lofdahl CG. Systemic CD4+ T-cell activation is correlated with FEV1 in smokers. Respir Med 2006;100:1088-93.
72. Roos-Engstrand E, Ekstrand-Hammarstrom B, Pourazar J, Behndig AE, Bucht A, Blomberg A. Influence of smoking cessation on airway T lymphocyte subsets in COPD. COPD 2009;6:112-20.
73. Saetta M, Baraldo S, Turato G, Beghe B, Casoni GL, Bellettato CM, et al. Increased proportion of CD8+ T-lymphocytes in the paratracheal lymph nodes of smokers with mild COPD. Sarcoidosis Vasc Diffuse Lung Dis 2003;20:28-32.
74. Tetley TD. Inflammatory cells and chronic obstructive pulmonary disease. Curr Drug Targets Inflamm Allergy 2005;4:607-18.
75. Freeman CM, Han MK, Martinez FJ, Murray S, Liu LX, Chensue SW, et al. Cytotoxic potential of lung CD8(+) T cells increases with chronic obstructive pulmonary disease severity and with in vitro stimulation by IL-18 or IL-15. J Immunol 2010;184:6650-13.
76. Tetley TD. Inflammatory cells and chronic obstructive pulmonary disease. Curr Drug Targets Inflamm Allergy 2005;4:607-18.
77. Maeno T, Houghton AM, Quintero PA, Grumelli S, Owen CA, Shapiro SD. CD8+ T cells are required for inflammation and destruction in cigarette smoke-induced emphysema in mice. J Immunol 2007;178:8090-6.
78. Hodge G, Mukaro V, Reynolds PN, Hodge S. Role of increased CD8/CD28(null) T cells and alternative co-stimulatory molecules in chronic obstructive pulmonary disease. Clin Exp Immunol 2011;166:94-102.
79. Hodge G, Jersmann H, Tran HB, Holmes M, Reynolds PN, Hodge S. Lymphocyte senescence in COPD is associated with loss of glucocorticoid receptor expression by pro-inflammatory/cytotoxic lymphocytes. Respir Res 2015;16:2.
83. Feghali-Bostwick CA, Gadgil AS, Otterbein LE, Pilewski JM, Stoner MW, Csizmadia E, et al. Autoantibodies in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:156-63.
84. Lambers C, Hacker S, Posch M, Hoetzenecker K, Pullreisz A, Lichtenauper M, et al. T cell senescence and contraction of T cell repertoire diversity in patients with chronic obstructive pulmonary disease. Clin Exp Immunol 2009;155:466-75.
85. Angulo M, Lecuona E, Sznejder JL. Role of MicroRNAs in lung disease. Arch Bronconeumol 2012;48:325-30.
86. De Smet EG, Mestdagh P, Vandesompele J, Brusselle GG, Bracke KR. Non-coding RNAs in the pathogenesis of COPD. Thorax 2015;70:782-91.
87. Rupani H, Sanchez-Elsner T, Howarth P. MicroRNAs and respiratory diseases. Eur Respir J 2013;41:695-705.
88. Ezzie ME, Crawford M, Cho JH, Orellana R, Zhang S, Gelinas R, et al. Gene expression networks in COPD: microRNA and mRNA regulation. Thorax 2012;67:122-31.
89. Savarimuthu Francis SM, Davidson MR, Tan ME, Wright CM, Clarke BE, Duhig EE, et al. MicroRNA-34c is associated with emphysema severity and modulates SERPANE1 expression. BMC Genomics 2014;15:88.
90. Van Pottelberge GR, Mestdagh P, Bracke KR, Thas O, van Durme YM, Joos GF, et al. MicroRNA expression in induced sputum of smokers and patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011;183:898-906.
91. Barnes PJ. Corticosteroid resistance in airway disease. Proc Am Thorac Soc 2004;1:264-8.
92. Di Stefano A, Caramori G, Ricciardolo FL, Capelli A, Adcock IM, Donner CF. Cellular and molecular mechanisms in chronic obstructive pulmonary disease: an overview. Clin Exp Allergy 2004;34:1156-67.
93. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet 2009;373:1905-17.
94. Barnes PJ, Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol 2013;131:636-45.
95. Wang M, Kumar RK, Foster PS. Pathogenesis of steroid-resistant airway hyperresponsiveness: interaction between IFN-gamma and TLR4/MyD88 pathways. J Immunol 2009;182:5107-15.
96. Li J, Wang W, Baines KI, Bowden NA, Hansbro PM, Gibson PG, et al. IL-27/IFN-gamma induce MyD88-dependent steroid-resistant airway hyperresponsiveness by inhibiting glucocorticoid signaling in macrophages. J Immunol 2010;185:4401-9.
97. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest 2008;118:3546-56.
98. Torviren M, Campbell H, Kilty L. The role of IFN-gamma in regulation of IFN-gamma-inducible protein 10 (IP-10) expression in lung epithelial cell and peripheral blood mononuclear cell co-cultures. Respir Res 2007;8:30.
99. Southworth T, Metryka A, Lea S, Farrow S, Plumb J, Singh D. IFN-gamma synergistically enhances LPS signalling in alveolar macrophages from COPD patients and controls by corticosteroid-resistant STAT1 activation. Br J Pharmacol 2012;166:2070-83.
100. Goleva E, Li LB, Leung DY. IFN-gamma reverses IL-2- and IL-4-mediated T-cell steroid resistance. Am J Respir Cell Mol Biol 2009;40:223-30.
101. Kaur M, Smyth LJ, Cadden P, Grundy S, Ray D, Plumb J, et al. T lymphocyte insensitivity to corticosteroids in chronic obstructive pulmonary disease. Respir Res 2012;13:20.