Current Trends in Biotechnology and Pharmacy
Vol. 17 (4A) 114 - 120, October 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.4s.98

Chronic inflammation diseases of the lungs

Audrey Siew Foong Kow[1,*] and Ming Tatt Lee[1,2]

[1]Faculty of Pharmaceutical Sciences, [2]Centre of Research for Mental Health and Wellbeing, UCSI University, Cheras 56000, Kuala Lumpur, Malaysia

*Corresponding author: audreykow@ucsiuniversity.edu.my

Abstract

Chronic inflammation is a low-grade, persistent, and non-resolving age-related condition that is associated with damage-associated molecular patterns, unlike acute inflammation. Driven by many factors such as chronic infections, lifestyle, exposure to environmental and industrial toxicants, and others, chronic inflammation increases the risk of metabolic diseases that are of burden to the healthcare system. Asthma and chronic obstructive pulmonary disease (COPD) are examples of chronic inflammation diseases affecting the lungs. These chronic respiratory diseases are exacerbations of acute inflammation due to the continual cycle of production and secretion of proinflammatory mediators, even without the initial stimulus. These proinflammatory mediators are secreted by different types of immune cells, making asthma and COPD taking a more heterogenous profile than initially thought. Through continuous research, asthma, which was initially thought to be mainly eosinophilic, has seen the involvement of mast cells and neutrophils. Similarly, with COPD, which is more neutrophilic, sees the involvement of macrophages and eosinophils. The following review briefly illustrates the roles of the different immune cells and proinflammatory mediators in asthma and COPD, highlighting the importance of continuous research that will help improve the management of these debilitating diseases.

Keywords: Chronic inflammation, asthma, chronic obstructive pulmonary disease

Chronic inflammation

Chronic inflammation is a form of inflammation that is slow and lasts for long periods that span from months to years. Several factors cause chronic inflammation – failure to remove infectious agents, being exposed to low levels of irritants that cannot be removed metabolically or phagocytosed, autoimmune disorders, defect in immune cells, recurrent episodes of acute inflammation, and the production of inducers of oxidative stress from inflammation (1).

Systemic chronic inflammation (SCI) differs from acute inflammation as it is triggered by damage-associated molecular patterns (DAMPs) such as exposome, metabolic dysfunction or tissue damage. SCI is classified as low-grade, persistent and non-resolving, and age-related (it increases with age) (2). SCI in older individuals is thought to be due to higher circulating levels of cytokines, chemokines, and acute phase proteins in addition to greater expression of inflammatory genes. Apart from that, there are numerous contributors to SCI. These include chronic infections, lifestyle, social and physical environment, physical activity, microbiome dysbiosis, diet, social and cultural changes, and exposure to environmental and industrial toxicants (2).

Chronic inflammation has been linked to increased risk of metabolic diseases termed as chronic inflammatory diseases. As stated by Furman et al. (2019)(2), more than 50% of all deaths are due to inflammation-related diseases. In this review, chronic inflammation diseases of the lungs - asthma and chronic obstructive pulmonary disease (COPD) are introduced.

Chronic inflammation and asthma

Asthma is characterized by breathlessness, wheezing, and airflow

obstruction. Asthma prevalence estimates for persons aged 5–69 years in 2019 range from 5.4% to 17.9% of the global population, depending on different definitions of asthma (3). Recent evidence has revealed that the development of asthma comes from the inappropriate activation of the immune system and the dysregulation of endogenous immune regulating processes (4). It is considered a chronic inflammation disorder because, after the initial exposure and activation, a repetitive cycle of tissue damage and inflammatory-cell recruitment persist even without the presence of sustained allergens (4). Figure 1 illustrates the summary of the relationship between chronic inflammation and asthma.

Asthma develops at the initial exposure to allergens that activate allergen-specific T-helper (Th) type-2 (Th2) lymphocytes and immunoglobulin E (IgE) synthesis. With each successive allergen exposure, inflammatory cells will be recruited, activated, and release proinflammatory mediators. For instance, the activation of Th2 cells leads to the release of interleukin (IL) -4, -13 and -5 (4). It is well known that IL-4 and IL-13 are involved in B cell class switching, which drives the synthesis of IgE (5).Being an immune cell with a high affinity for IgE, mast cells are known to play an important role in the pathogenesis of asthma. The crosslinking of allergens and receptor bound IgE present on the surfaces of mast cells triggers a cascade of intracellular signalling events that brings about the symptoms of asthma. Preformed mediators such as proteases, histamines, lipid-derived eicosanoids, leukotrienes, and prostaglandins cause early phase asthmatic reaction which then leads to late phase asthmatic reaction, which is driven by Th2 eosinophilic inflammation. The majority of IgE in the asthmatic airways is bound by high affinity IgE receptor 1 (FcεR1) found on mast cells. The mast cells can produce a variety of proinflammatory mediators such as IL-4 and IL-13 (4). Both IL-4 and IL-13 trigger the production of mucus and excessive mucus will obstruct the airways (5). IL-4 and IL-13 may act upon the airway smooth muscles cells causing hypercontractility of the cells and inducing the

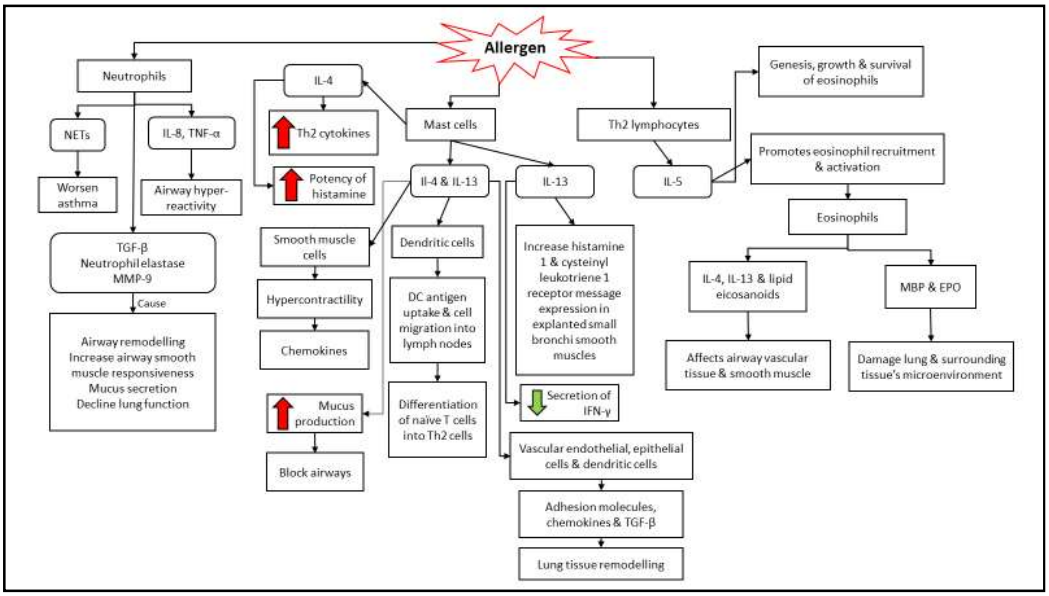

Figure 1: Chronic inflammation and asthma. Initial exposure to allergen activates neutrophils, mast cells, Th2 lymphocytes releasing multiple cytokines such as IL-4, IL-13, IL-5 and others. The production of these mediators and other proteins contribute to the symptoms of asthma such as airway remodelling, lung tissue remodelling, ans blocked airways.

Chronic inflammation diseases of the lungs

Vol. 17 (4A) 114 - 120, October 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.4s.98

release of chemokines. Apart from that, they also trigger the release of adhesion molecules, chemokines, and transforming growth factor beta (TGF-β) from vascular endothelial and airway epithelial cells (5). Manson et al also reported that IL-4 can increase the potency of histamine, while IL-13 was seen to increase histamine 1 and cysteinyl leukotriene 1 receptor message expression in explanted small bronchi smooth muscles, increasing the airway cells' responsiveness, which leads to symptoms of asthma (6).

Furthermore, the effects of IL-4 and IL-13 were reported on dendritic cells (DC). Both increase DC antigen uptake and cell migration into the lymph nodes, driving the differentiation of naïve T cells into Th2 cells. Besides that, it was reported that IL-4 can increase the secretion of Th2 cytokines while IL-13 can suppress the secretion of interferon gamma (IFN-γ) in mice by enhancing the capacity of DCs' effects on T cells. On top of that, both IL-4 and IL-13 indirectly remodel the lungs of chronic asthmatics through the production of adhesion molecules, chemokines and cytokines which stimulate the secretion of TGF-β1. The expression of these molecules also contributes to the influx of other circulating inflammatory cells, which play a role in lung tissue remodelling (5).

Activation of Th2 cells also releases IL-5, as do mast cells. IL-5 is important in promoting eosinophil recruitment and activation(4). They are also needed in the genesis, growth, and survival of eosinophils (5). The involvement of eosinophilic inflammation in asthma is well known; granulotytic eosinophils are found in abundance in atopic allergic inflammatory infiltrates, as noted by Kay (2005)(7). Recruited from the bone marrow as $CD34^+$ precursors by prostaglandins, cysteinyl leukotrienes, cytokines, and chemokines, these primed eosinophils will degranulate and release major basic protein (MBP) and eosinophil peroxidase (EPO). Although these cationic proteins protect one from parasitic worms, they unfortunately damage the lung and surrounding tissue's microenvironment. In addition, activated eosinophils also release Th2 cytokines such as IL-4 and IL-13, and lipid eicosanoids, which affect the airway vascular tissue and smooth muscle (4,5).

High level of plasma IL-6 in allergic asthma patients was reported by Wong et al. (2001)(8) and negative correlation between IL-6 levels and forced expiratory volume was observed by Morjaria et al. (2011)(9). Experimental asthma studies have shown that IL-6 can control the influx of $CD4^+$ T lymphocytes to the airways, and its signalling was needed to expand and proliferate effector Th2 cells in the airways. In addition, IL-6 also modulate local regulatory $CD4^+CD25^+$ T cell survival and control the initial Th2 cell development in the lung (10).

Along with mast cells and eosinophils, neutrophils are also implicated in asthma. High numbers of sputum neutrophils are reported in severe asthmatics who were prescribed with high levels of inhaled and systemic corticosteroids. Several mediators are found to be associated with neutrophilic airway inflammation, and CXCL8 (IL-8) is the most potent mediator (11). IL-8 is secreted by various cell types, including neutrophils, and this is possible, as shown by Gounni et al. (2001)(12). They found that neutrophils in asthmatic patients express FcεR1 and upon crosslinking and activation, IL-8 will be released (11). Apart from IL-8, increased tumor necrosis factor alpha (TNF-α) level was also noted in airways of asthma patients and Thomas et al (1995)(13) had previously demonstrated that by exposing normal subjects to TNF-α, airway hyper-reactivity was induced, and they also recorded an increased of sputum neutrophil counts. The additional implication of neutrophils in asthmatics is likely due to neutrophil extracellular traps (NETs) released. Although NETs have antimicrobial effects, their secretion could be induced by proinflammatory mediators too and they will worsen asthma and COPD (11,14,15). Additionally, neutrophils could cause airway remodelling, mucus hypersecretion, increased airway smooth muscle responsiveness and rapid decline in

lung function. All these events are mediated by TGF-β, neutrophil elastase, and neutrophil-generated matrix metalloprotease-9. Neutrophil elastase also enhances the production of IL-8 from epithelial cells which will then increase the recruitment of neutrophils to the airways. This continuous cycle clearly depicts the effects of inflammation on asthma without allergens.

Chronic inflammation and chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD), which is often associated with cigarette smoke exposure, is characterized by a progressive and irreversible decline in lung function due to obstructed airflow, destroyed parenchyma, and emphysema. It is also an example of inflammatory disease of the airways (16). In 2019, the global prevalence of COPD among patients aged 30–79 was 10.3%, which can be estimated to affect 391.9 million people (17). Elevated numbers of neutrophils, macrophages, B cells, CD4+ T cells, CD8+ T cells, dendritic cells, and eosinophils are observed in COPD patients (18), where macrophages play an important role (19). The severity of COPD parallels the increased number of CD8+ T cells, where these cells release proteolytic enzymes causing apoptosis of structural cells. Though the involvement of CD4+ T cells, B cells, and dendritic cells in COPD is still vague, their presence is seen in COPD lungs and experimental models ofchronic cigarette smoke-exposed subjects (20).

Macrophages are found in abundance in COPD patients because of increased recruitment of monocytes or increased proliferation and prolonged survival in the lungs (16). The activation of macrophages by cigarette smoke or other noxious unknown particles releases several proinflammatory medicators and chemotactic factors. They include TNF-α, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), leukotriene (LT) B4 and reactive oxygen species (ROS). On top of that, proteolytic enzymes such as matrix metalloproteinase (MMP)-9 and MMP-12 are also secreted.These mediators all contributed to the development of pulmonary emphysema(19). Cigarette smoke exposure also compromises the function of macrophages creating a microenvironment which is dominated by free radicals which affects the phagocytosis of bacteria (as evidenced in 50% of COPD patients who are chronically colonized with *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*) and efferocytosis of apoptotic cells (20).

Besides causing pulmonary emphysema to develop, the secreted IL-8 and LTB4 also trigger the recruitment of neutrophils. Recruited neutrophils will enter the airways, and they are upregulated on endothelial cells in the airways. Under the direction of IL-8 and LTB4, adherent neutrophils will migrate into the respiratory tract, and their survival here is driven by cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF). Neutrophils destroy COPD patients' alveolar through the secretion of serine proteases which include neutrophil elastase, cathepsin G, proteinase-3, MMP-8, and MMP-9. In addition, these serine proteases also stimulates mucus production (16). The presence of neutrophilic inflammation in COPD patients even though they have stopped smoking at least 1 year is likely due to the continuous recruitment of leukocytes into the airways (20).

Epithelial cells are also triggered in COPD patients. Activated epithelial cells also produce several proinflammatory mediators, such as TNF-α, IL-1β, GM-CSF, and IL-8. Apart from the mediators secreted, epithelial cells in the small airways could also secrete TGF-β which causes local fibrosis (16). Besides activating fibroblasts and small airway fibrosis, activated epithelial cells lead to squamous metaplasia, disruption of their antimicrobial activity, and metaplasia of the submucosal gland and goblet cells (19). The activation of airway epithelial cells as triggered by cigarette smoke and virus infection, also

Vol. 17 (4A) 114 - 120, October 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.4s.98

releases the upstream cytokines thymic stomal lymphopoietin (TSLP) and IL-33. This in turn recruits Th2 and type 2 innate lymphoid cells (ILC2) and secretes IL-5, leading to eosinophilic inflammation (21).

ROS are also produced by the macrophages, neutrophils, eosinophils, and epithelial cells in COPD, causing the imbalance between antioxidants and active oxygen radicals. This imbalance brings about serious damage to lipids, proteins, and cell deoxyribonucleic acid (DNA)(19).

Several hypotheses were proposed on the persistent inflammation that leads to COPD, especially in smokers, and the involvement of age. Tzortzaki and Siafakas (2009)(22) proposed that persistent activation of the host immune system was due to the recognition of alveolar cells that carry mutated genes as “non-self” by dendritic cells. The mutation may have developed due to oxidative DNA damage from exposure to tobacco smoke. On another note, a two-hit hypothesis for chronic inflammation in COPD, which results from the activation of the DNA damage response and senescence-associated secretory phenotype (SASP) was proposed by Aoshiba et al. (2013)(23). Other theories implicating chronic inflammation in COPD include one’s autoimmunity through the amplification of the positive-feedback loop between inflammation and autoreactive conditions (23–25), chronic infection (23,26), and the ageing body with reduced immunity in general (23,27).

In the two-hit hypothesis, Aoshiba et al. (2013)(23)explained thatin smokers primarily, the first hit is recognisedas tobacco smoke. Tobacco smoke will first trigger the initial inflammation in the lungs. This was also supported by previous observations by Cosio et al. (2009)(25). On the second hit, which is hypothesized in susceptible smokers, COPD develops because of DNA damage. This induces apoptosis and senescence thus

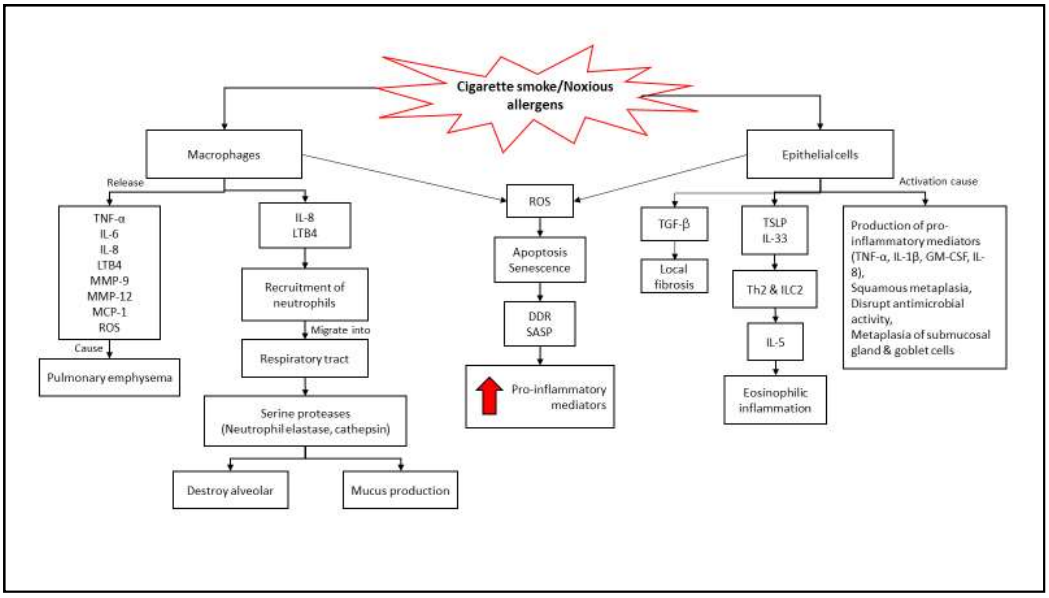

Figure 2: Chronic inflammation and COPD. On the exposure to cigarette smoke or noxious allergens, macrophages and epithelial cells will be activated. The activation of these cells causes the release of pro-inflammatory cytokines such as TNF-α, ILs, MMPs, TSLP, and ROS. These cytokines cause pulmonary emphysema, the main characteristic of COPD, and other symptoms such as metaplasia. Release of IL-8 and LTB4 also causes the recruitment of neutrophils leading to neutrophilic inflammation as seen in some COPD cases.

activating DNA damage response (DDR) and SASP leading to further secretion of proinflammatory mediators. Susceptible smokers refer to those who develop DNA damage such as double-strand breaks in the airways and alveolar cells because of more severe inflammatory cell infiltration and larger amounts of ROS/reactive nitrogen species (RNS) which then activate DDR, apoptosis, senescence and SASP and eventually proinflammatory mediators' secretion. A positive-feedback mechanism will develop as triggered by the proinflammatory mediators, enhancing the infiltration of inflammatory cells that further stimulate the production of ROS/RNS, activation of DDR and so on. This in turn establishes the vicious cycle between inflammation and DNA damage, leading to chronic inflammation and eventually COPD (23). Figure 2 summarizes the events that happen upon cigarette smoke or noxious allergens' exposure.

Conclusion

Asthma and COPD are examples of chronic inflammation disorders of the lungs that happen due to the vicious cycle between inflammation from the initial activation and the continuous secretion of proinflammatory meditaors in the absence of the trigger. Although asthma has an eosinophilic inflammation distict profile and COPD is mainly neutrophilic, both disorders also have a heterogenous profile involving more and sometimes all the inflammatory cells. Furthermore, it is estimated that 20% of COPD patients exhibited pathological features of asthma (28). Due to this complexity, it is always a challenge to develop a one-for-all treatment. Hence, continuous research to understand the mechanisms opens the doors to developing better ways to manage these disorders.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgement

The study was supported byUCSI University Research Excellence and Innovation Grant, Malaysia (REIG-FPS-2022/006).

References

1. Pahwa R, Goyal A, Jialal I. (2023) Chronic Inflammation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing

2. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. (2019) Chronic inflammation in the etiology of disease across the life span, Nature Medicine. 25(12):1822–32.

3. Song P, Adeloye D, Salim H, Dos Santos JP, Campbell H, Sheikh A, et al. (2022) Global, regional, and national prevalence of asthma in 2019: a systematic analysis and modelling study, Journal of Global Health.12:04052.

4. Murdoch JR, Lloyd CM. (2010) Chronic inflammation and asthma, Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis.690(1):24–39.

5. Becerra-Díaz M, Wills-Karp M, Heller NM. (2017) New perspectives on the regulation of type II inflammation in asthma, F1000Res.6:1014.

6. Manson ML, Säfholm J, James A, Johnsson AK, Bergman P, Al-Ameri M, et al. (2020) IL-13 and IL-4, but not IL-5 nor IL-17A, induce hyperresponsiveness in isolated human small airways, Journal of Allergy and Clinical Immunology. 145(3):808-817.e2.

7. Kay AB. (2005) The role of eosinophils in the pathogenesis of asthma, Trends in Molecular Medicine. 11(4):148–52.

8. Wong CK, Ho CY, Ko FWS, Chan CHS, Ho ASS, Hui DSC, et al. (2001) Proinflammatory cytokines (IL-17, IL-6, IL-18 and IL-12) and Th cytokines (IFN-γ, IL-4, IL-10 and IL-13) in patients with allergic asthma, Clinical and Experimental Immunology.125(2):177–83.

9. Morjaria JB, Babu KS, Vijayanand P, Chauhan AJ, Davies DE, Holgate ST. (2011) Sputum IL-6 concentrations in severe asthma and its relationship with FEV1, Thorax.66(6):537–537.

10. Neurath MF, Finotto S. (2011) IL-6 signaling in autoimmunity, chronic inflammation and inflammation-associated cancer, Cytokine & Growth Factor Reviews. 22(2):83–9.

11. Ray A, Kolls JK. (2017) Neutrophilic Inflammation in Asthma and Association with Disease Severity, Trends in Immunology.38(12):942–54.

12. Gounni AS, Lamkhioued B, Koussih L, Ra C, Renzi PM, Hamid Q. (2001) Human neutrophils express the high-affinity receptor for immunoglobulin E (FcεRI): Role in asthma, FASEB Journal. 15(6):940–9.

13. Thomas PS, Yates DH, Barnes PJ. (1995) Tumor necrosis factor-alpha increases airway responsiveness and sputum neutrophilia in normal human subjects. American Journal of Respiratory and Critical Care Medicine.152(1):76–80.

14. Dworski R, Simon HU, Hoskins A, Yousefi S. (2011) Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways, Journal of Allergy and Clinical Immunology.127(5):1260–6.

15. Grabcanovic-Musija F, Obermayer A, Stoiber W, Krautgartner WD, Steinbacher P, Winterberg N, et al. (2015) Neutrophil extracellular trap (NET) formation characterises stable and exacerbated COPD and correlates with airflow limitation, Respiratory Research. 16(1).

16. Rovina N, Koutsoukou A, Koulouris NG. (2013) Inflammation and Immune Response in COPD: Where Do We Stand? Mediators of Inflammation. 2013:e413735.

17. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I, et al. (2022) Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis, The Lancet Respiratory Medicine. 10(5):447–58.

18. Yao H, Rahman I. (2009) Current concepts on the role of inflammation in COPD and lung cancer, Current Opinion in Pharmacology.9(4):375–83.

19. Angelis N, Porpodis K, Zarogoulidis P, Spyratos D, Kioumis I, Papaiwannou A, et al. (2014) Airway inflammation in chronic obstructive pulmonary disease, Journal of Thoracic Disiease.6(Suppl 1):S167–72.

20. Bozinovski S, Anthony D, Vlahos R. (2014) Targeting pro-resolution pathways to combat chronic inflammation in COPD. Journal of Thoracic Disease.6(11):1548–56.

21. Barnes PJ. (2019) Inflammatory endotypes in COPD, Allergy.74(7):1249–56.

22. Tzortzaki EG, Siafakas NM. (2009) A hypothesis for the initiation of COPD. European Respiratory Journal.34(2):310–5.

23. Aoshiba K, Tsuji T, Yamaguchi K, Itoh M, Nakamura H. (2013) The danger signal plus DNA damage two-hit hypothesis for chronic inflammation in COPD, European Respiratory Journal.42(6):1689–95.

24. Bolland S, Garcia-Sastre A. (2009) Vicious circle: systemic autoreactivity in Ro52/TRIM21-deficient mice, Journal of Experimental Medicine.206(8):1647–51.

25. Cosio MG, Saetta M, Agusti A. (2009) Immunologic aspects of chronic obstructive pulmonary disease, The New England Journal of Medicine. 360(23):2445–54.

26. Sethi S. (2000) Bacterial infection and the pathogenesis of COPD, Chest. 117(5 Suppl 1):286S-91S.

27. Lee N, Shin MS, Kang I. (2012) T-cell biology in aging, with a focus on lung disease, The Journals of Gerontology Series A, Biological Sciences and Medical Sciences. 67(3):254–63.

28. Gibson PG, McDonald VM. (2015) Asthma-COPD overlap 2015: now we are six, Thorax. 70(7):683–91.