Chapter

# The Immune Response in the Pathophysiology of Pulmonary Diseases

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## Abstract

Chronic obstructive pulmonary disease (COPD) is the world's third leading cause of death. The number of patients with asthma is increasing in developed countries. We review here the main features of pathophysiology in these obstructive diseases. Tobacco smoke and other air pollution stimulate chronic inflammation in COPD. Asthma is a type 1 hypersensitivity that is a response to various allergens. In both pathologies, chronic inflammatory response leads to airway remodeling, significantly impacting lung function and a patient's daily activity. Besides imaging techniques, a critical diagnostic tool is a pulmonary function test with characteristic obstructive patterns and respiratory symptoms. Sarcoidosis is discussed as an example of a restrictive disease. Finally, we shortly highlight the direction of current research.

**Keywords:** inflammation, chronic obstructive pulmonary disease, asthma, sarcoidosis, lung functional test

## 1. Introduction

### 1.1 The innate and adaptive inflammatory response in the lung

The inflammatory response is innate and adaptive, contributing to pulmonary diseases [1, 2]. During evolution, the human immune system "learned" to recognize and remember some common pathogens whose general features induce the innate immune response. Thus, the first component is considered to be congenital, non-specific and prompt. It includes the activation of phagocytic cells, mainly granulocytes, and complement. The adaptive immune response is associated with the ability of cells to present antigens in the complex with MHC molecule. The other component is an evolutionary younger, acquired and specific one.

In the lung, the resident macrophages phagocyte/engulf various antigens/pathogens with two aims; they kill an intruder and apprise the other immune cells (mainly T cells) about the specific character of the intruder. Latter happens in the process called antigen presentation; the engulfed antigen is processed in the endoplasmic reticulum and then sent to the cellular surface in the complex with MHC class II. This complex is recognized by naïve T cells that, in turn, proliferate and differentiate in

other to multiply and specify the immune response based on the particular antigen/pathogen origin [3]. Under normal conditions, there is prevailing proportion of alveolar macrophages in bronchoalveolar lavage. However, their absolute number is not high, and they do not have any immune-histological activation features [4]. Various pathologies are associated with their stimulation and activation of T cells, whose numbers are then elevated [5]. In addition, other immune cells are delivered from the circulation via subepithelial vessels in small airways [3].

All granulocytes can phagocyte antigens/pathogens, but they cannot present antigens as macrophages or other antigen-presenting cells (APC), e.g. dendritic cells. Though granulocyte can bind antigen via a toll-like receptor (TLR) on their cellular membrane, it is not called an antigen presentation because the bound antigen was not processed in the endoplasmic reticulum. Among granulocytes, the neutrophils are the most typical phagocytes. They are the most important cellular component of the innate immune response against bacterial infection, including pulmonary one. In asthma, the allergic response is typically associated with the activation of other granulocytes,

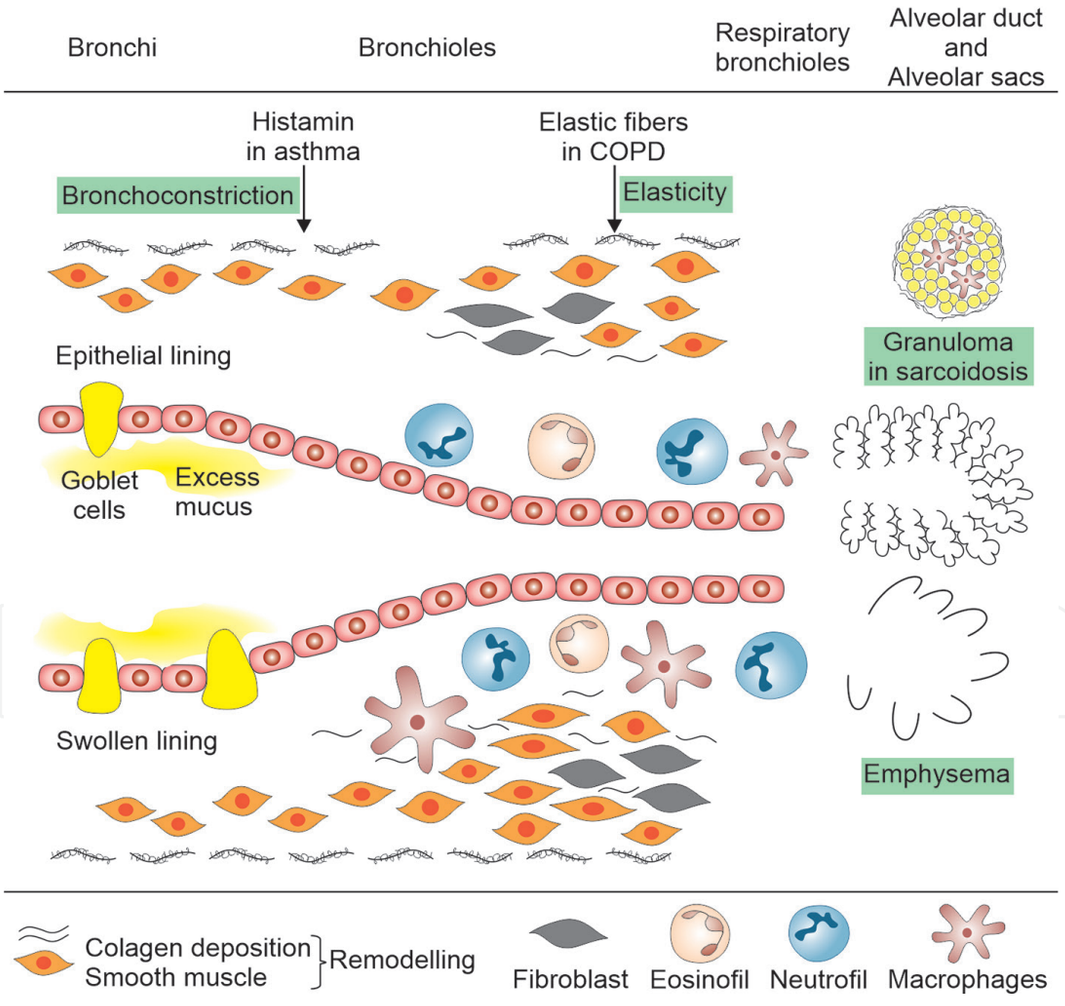


**Figure 1.**
*The immune response in chronic obstructive pulmonary disease (COPD), asthma and sarcoidosis. Legend: In asthma, type 1 hypersensitivity causes reversible airway limitation by histamine-mediated bronchoconstriction, excess mucus, swollen lining, and chronic remodeling. In COPD, the inflammation causes slightly reversible airway limitation due to swollen lining, excess mucus, and chronic remodeling with decreased lung elasticity. The intensive degradation of the extracellular matrix obliterates the alveolar septa in emphysema. In sarcoidosis, lung restriction is due to the sarcoid granuloma.*

including mast cells (tissue form of basophils) and eosinophils (see **Figure 1**). However, neutrophils and other cells can also contribute to some asthmatic phenotypes [6, 7]. Both alveolar macrophages and neutrophils are elevated in bronchoalveolar lavage obtained from patient with chronic obstructive pulmonary disease (COPD). The contribution of eosinophils is also discussed in COPD [8].

### 1.2 The effect of the immune response on the lung function

Intensive or chronic pulmonary inflammation has reversible or even irreversible effects on lung function showing various changes in spirometry investigation [9]. **Table 1** summarizes the main spirometry parameters. Generally, we recognize two patterns; obstructive and restrictive; see **Figure 2**.

Obstructive diseases primarily affect the airways where inflammation is localized. The pulmonary parenchyma is not involved. See **Figure 1**. Thus diffusion capacity of oxygen is assessed as the diffusion capacity carbon monoxide (DLCO) is usually normal. Due to airway obstruction, the first manifestation is expiratory difficulties showing low forced expiratory volume in 1 second (FEV1). The accumulated air does not contribute to gas exchange between the alveoli and blood. It creates a dead space increasing residual volume (RV) and secondarily functional residual capacity (FRC) and total lung capacity (TLC); both parameters involve RV. Because forced vital capacity (FVC) is usually normal or maybe only slightly reduced than FEV1 value, the ratio of FEV1 and FVC is decreased and considered as a more reliable marker than low FEV1 alone [9, 10].

In restrictive diseases, the inflammation affects the lung parenchyma and prolongs oxygen diffusion distance. Thus DLCO and compliance are usually decreased [9, 11]. The patients have inspiratory and expiratory difficulties because TLC is low. Both FEV1 and FVC are decreased at a similar rate, or FVC is decreased even more than FEV1. The ratio of FEV1 and FVC is, therefore, normal or elevated. TLC is decreased because of both low RV and low FRC.

Comparison between obstructive and restrictive diseases further shows that the formal one is frequently associated with hypercapnia (respiratory insufficiency type II), and the latter is associated with normocapnia (respiratory insufficiency type I). However, it greatly depends on the presence/absence of hyperventilation and hypoventilation.

Hypoxemia is present in all (obstructive and restrictive) pulmonary diseases and results from two typical mechanisms or their combination. They are shunting and dead space; both refer to a mismatch between the alveoli's perfusion (Q) and ventilation (V). Ideally, the ratio between V and Q must equal one to ensure the best gas exchange efficiency between blood and alveoli. Shunting refers to a low V/Q due to either too little ventilation or too much blood flow or both. Latter is common in pulmonary oedema because perfusion must deliver other immune cells from the circulation. One of the most typical examples is pneumonia. Interstitial pneumonia also coexists with pulmonary sarcoidosis.

Dead space refers to a high V/Q due to too much ventilation or too little blood flow or both. Typical examples of dead space are decreased perfusion in air embolism or air trapping in obstructive diseases. The latter results from the chronic inflammation and subsequent proteolytic degradation of the elastic fibers in the airways. First, a physiological role of elastic fibers will be mentioned here [12].

Briefly, as we do not have a primary expiratory muscle (compared to the diaphragm being a primary inspiratory muscle), the quiet expiration at rest is a passive mechanism that is provided by elastic fibers and their recoil. Besides non-energetic

| Parameter | | Obstructive | Restrictive | Note |
|---|---|---|---|---|
| Flow-volume loop | | | | |
| FEV1 | Forced expiratory volume in 1 second | ↓ | ↓ | Volume exhaled in the first second |
| FVC (VC) | Forced vital capacity (vital capacity) | – or ↓ | ↓ or ↓↓ | Maximal amount of air that the patient can forcibly exhale after taking a maximal inhalation* |
| FEV1/FVC | | ↓ | – or ↑ | |
| PEF | Peal expiratory flow | ↓ | ↓ | Maximal speed of airflow as the patient exhales |
| Body plethysmography | | | | |
| RV | Residual volume | ↑ | ↓ | Volume of gas remaining in the lungs following a maximal exhalation |
| TLC | Total lung capacity | ↑ | ↓ | Amount of gas contained in the lung at maximal inspiration |
| FRC | Functional residual capacity | ↑ | ↓ | Volume remaining in the lungs after a normal, passive exhalation. |
| Diffusion | | | | |
| DLCO | Diffusion capacity of CO | — | ↓ | Diffusion capacity of carbon monoxide |

*Legend: ↓; decreased, ↑; increased, –; normal.* (Maximal volume of gas that can be expelled from the lungs by a forceful effort following maximal inspiration).*

**Table 1.**
*The comparison of the lung functional test between obstructive and restrictive pulmonary diseases.*

demand, the other advantage is that the elastic recoil increases pressure in the alveoli without increasing intrapleural pressure during expiration. The intra-alveolar pressure is, therefore, higher than that surrounding the alveoli and small airways during quiet expiration. This mechanism impedes air trapping; in other words, alveoli and small airways collapse under excessive external expiratory pressure.

On the other hand, some small extent of short-term air trapping happens even in healthy lungs. A typical situation is a physical exercise when the accessory expiratory muscles must help with the forced expiration creating positive intrapleural pressure. Then the small airways collapse due to the high external pressure surrounding them, air trapping [12].

The issue is that obstructive diseases such as COPD damage elastic fibers and their recoil. The poor elastic recoil means that the accessory expiratory muscles must substitute it and work more constantly (not only during physical activity) in the patients. Unfortunately, they also impose an external/intrapleural pressure higher than that in the small airways without the contribution from elastic fibers in the airway wall. Thus, COPD is a typical example of air trapping contributing to air accumulation; dead space.

The following text outlines the immune response in the pathophysiology of two obstructive diseases (COPD and asthma) and one restrictive disease (sarcoidosis).

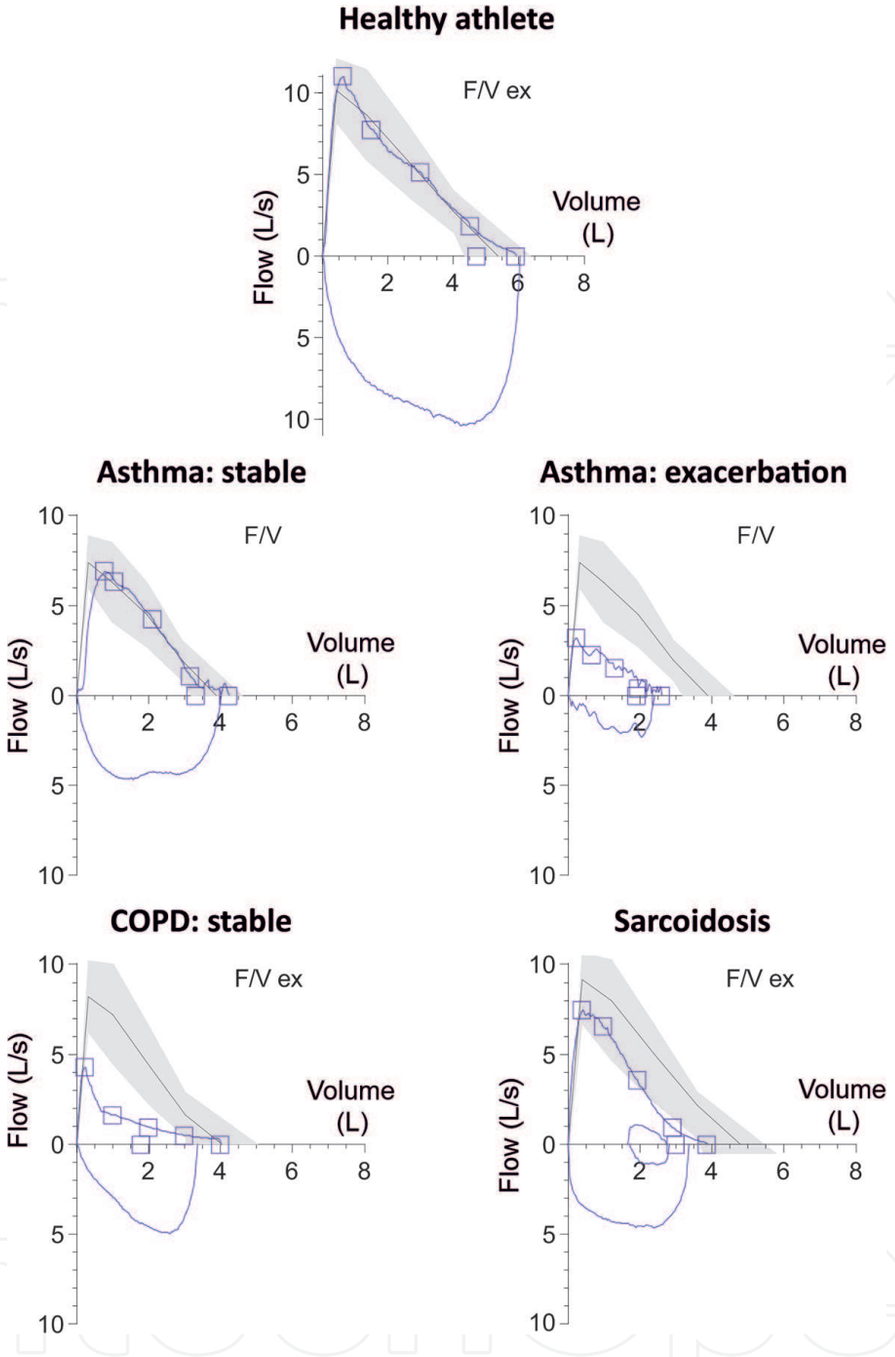


**Figure 2.**
*The lung functional test in COPD, asthma, asthma with exacerbation and sarcoidosis.*

## 2. COPD

### 2.1 Definition

Chronic obstructive pulmonary disease (COPD) is a common, preventable, treatable disease usually caused by significant exposure to noxious particles or gases (mainly tobacco smoke). COPD patients suffer from persistent respiratory symptoms (dyspnea, particularly during physical activity and chronic cough with/without sputum production) and airflow limitation due to the pathological

abnormalities of airways (bronchitis and obstructive bronchiolitis) and alveoli (emphysema) [10, 13–15].

Besides clinical presentation (symptoms) and history of air pollution exposure (a risk factor), diagnosis of COPD requires spirometry, typically showing not fully reversible airflow limitation (FEV1/FVC < 0.7 post-bronchodilation). Clinical assessments include lung diffusing capacity (DLco) and computed tomography, mainly in emphysema. The patients frequently have other comorbid diseases (cardiovascular diseases, bronchiectasis, osteoporosis, gastroesophageal reflux, muscle mass loss, lung cancer) and thus require other specific investigations.

## 2.2 Pathophysiology in COPD

A leading cause of COPD is tobacco smoking inducing chronic inflammation in the lung. Neutrophils are critical cells in the pathogenesis of COPD. In response to inhaled air pollution, neutrophils accumulate in the lung and airways of COPD patients, and they release reactive oxygen species (ROS, e.g. hydrogen peroxide), serine proteases (e.g. neutrophil elastase), matrix metalloproteinases (MMPs) and other pro-inflammatory factors. Alveolar macrophages are another important source of ROS and MMPs in COPD [1]. The aberrant oxidative stress and the excessive proteinase activity contribute together to the proteolytic degradation of elastic components in the COPD lung. In turn, low elastic recoil decreases the ability of the airways to remain open during expiration in COPD patients. The pulmonary functional test, therefore, shows a limitation of maximal airflow rate during forced expiration, usually measured by forced expiratory volume at 1 second (FEV1) [16].

Besides the loss of elasticity in COPD, the small airways are narrowed due to the increased thickness of the airway wall. This happens because the fibroblasts are activated to synthesize collagen and other structural proteins that are deposited mainly in the airway wall. The airway remodeling in COPD also includes the increased mass of airway smooth muscles and mucosal hyperproduction with decreased clearance due to mucociliary dysfunction. In particular, MUC5B produced by secretory cells in the airways is elevated and contributes to airway occlusion in COPD patients. Poor ciliary function may contribute to developing microbial or viral exacerbations in COPD patients [17].

## 2.3 Phenotypes in COPD

The primary classification includes two phenotypes: emphysema (a pink puffer) and chronic bronchitis (a blue bloater). Pulmonary emphysema is characterized by abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles and by the destroying the gas-exchanging surfaces (alveoli) without prominent fibrosis. A common manifestation is a dyspnea. The pulmonary function shows a low diffuse capacity (DLCO) because the obliterated alveolar septa are reducing the surface area in the lung. The patient's lungs have high compliance and elevated TLC (total lung capacity) due to a dead space; high residual volume (RV) contributes to TLC and functional residual capacity (FRC) much more than average RV in healthy lungs. Thus typical feature is hyperinflation and a barrel chest with a low, flattened diaphragm. The patients are usually cachectic because more energy is consumed for simple respiration. They must constantly use accessory muscles to ensure more extensiver changes in thoracic pressure. They often use pursed-lip breathing. This manoeuver prolongs and keeps sufficient airway pressure during constant effortful

expiration, thus decreasing air trapping imposed by accessory expiratory muscles. Pneumothorax is a common complication of emphysema.

The emphysema associated with COPD is also called centriacinar one, as only the central part of an acinus is involved (not the entire acinus). It differs from panacinar emphysema, which affects an entire acinus. The patients with panacinar emphysema have genetically driven alpha-1-antitrypsin deficiency (panacinar emphysema). They have similar manifestations as those with COPD-associated (centriacinar) emphysema, even without air pollution or smoking [18, 19].

The other phenotype is COPD accompanied by chronic bronchitis. Like panacinar emphysema with alpha-1-antitrypsin deficiency, chronic bronchitis can occur independetly without COPD. Then, it is defined as the presence of cough and sputum production for at least three months in each of two consecutive years. The chronic productive cough with purulent sputum is also the most typical manifestation of COPD-associated chronic bronchitis. Unlike a pink puffer (emphysema in COPD), a blue bloater (chronic bronchitis in COPD) usually has more severe hypoxemia that secondarily induces polycythemia and pulmonary hypertension and eventually leads to cor pulmonale.

At present, many new phenotypes have been recognized in COPD. Here, I select one termed COPD associated with frequent exacerbations. An exacerbation is an acute episode characterized by altered baseline dyspnea, cough, and/or sputum and beyond normal day-to-day variations during the stable course of COPD. GOLD 2023 introduced an even more specific definition that describes an exacerbation as: "an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the airways" [15]. These episodes are clinically relevant because they negatively impact the patient's health status [20].

### 2.4 The current research in COPD

The current review by Serban et al. summarizes several promising biomarkers in COPD [21]. Namely, a prognostic biomarker would be of great value. It is well established that early recognition of symptoms and the application of prompt therapy in patients with exacerbation (ECOPD) leads to a faster recovery, reduces the risk of hospitalization, and is associated with a better quality of life.

For instance, the relationship between matrix metalloproteinase (MMP)-9 concentration and frequent ECOPDs was reported in genetically driven alpha-1-antitrypsin deficiency (AATD)-associated emphysema [22]. So far, the prognostic relevance of MMP-9 was not confirmed by other studies on AATD-associated emphysema. Another study, however, reported the same biomarker (MMP-9) increasing the risk of future ECOPD in two large cohorts of COPD patients (COPDGene and ECLIPSE cohort) [23].

Regarding the prediction of future lung function, MMP-9, club cell secretory protein 16 (CC16), C-reactive protein (CRP) and IL-6 were associated with accelerated FEV1 decline [24–26]. In line with its anti-inflammatory property, the reduced level of serum CC16 in the future rapid decliners was reported consistently in two studies even [27]. However, another study did not confirm this observation [28]. Likewise, the elevated CRP was not associated with the future rapid decline in all studies [29]. Zemans et al. used a more complex approach of several biomarkers to improve data reliability. They reported the combination of three biomarkers

(CC16, fibrinogen, and sRAGE) associated with accelerated FEV1 decline and progression of emphysema in COPDGene and ECLIPSE cohorts [30]. In 2023, DiLillo et al. studied even more candidates and suggested that the complement system can predict individuals at risk for accelerated lung function decline (FEV1 decline ≥70 mL/year) ~ 6 years [31].

Castaldi et al. summarize that, ongoing longitudinal characterization of subjects in COPDGene will provide useful insights about the relationship between lung imaging parameters, molecular markers, and COPD progression that will enable the identification of subtypes based on underlying disease processes and distinct patterns of disease progression, with the potential to improve the clinical relevance and reproducibility of COPD subtypes [32].

## 3. Asthma

### 3.1 Definition

Asthma is a heterogeneous disease associated with chronic airway inflammation predominantly localized in the submucosal regions of the small airways of the lung. The diagnosis of asthma is based on the patient's symptoms, such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity. These symptoms are triggered by various factors such as allergen exposure, exercise or respiratory infections.

The diagnosis must be confirmed by variable/reversible airflow limitation according to spirometric measurements of lung function [33]; Forced Expiratory Volume in 1 second (FEV1) and, namely, its ratio to forced vital capacity (FVC) are reduced but improved after a bronchodilator is applied (reversibility responsiveness = hyperresponsiveness).

### 3.2 Pathophysiology in asthma

Various stimuli can trigger the airway inflammation that causes an episode of an asthma attack. In allergic asthma, exposure to house dust mites, air pollution, and other environmental antigens is the most common trigger. They induce the Type 1 hypersensitivity reaction that is mediated by an antigen-specific Immunoglobulin (Ig) E [34–36].

During an early asthmatic response, the IgE is induced and rapidly binds to its high-affinity FcεRI receptor on the mast cells and basophils to sensitize an individual to the antigen. The following exposure leads to the antigen cross-link two molecules of IgE-FcεRI receptor complexes resulting in the degranulation of the mast cells. The mechanisms of IgE production are not clear but involve T-helper (Th) 2 cells producing interleukin (IL)-4 and IL-13. Other cells include the type 2 innate lymphoid cells (ILC2), producing IL-5, IL-9 and IL-13 upon stimulation by IL-33 [35].

The most potent product of the degranulation is histamine inducing three responses: bronchial smooth muscle contraction (bronchospasm) reducing airflow and vasodilation with increased capillary permeability causing mucosal oedema and mucus secretion from mucosal goblet cells plugging the airways. These lead together to the acute narrowing of the airways. After the early asthmatic response, the late response can develop involving other leukocytes of the innate immune response (e.g. eosinophils and neutrophils). Their products (e.g. leukotrienes, proteolytic

enzymes and inflammatory cytokines) further damage the lung tissue and prolong smooth muscle constriction [35, 36]. It manifests itself as an acute asthmatic exacerbation or attack.

According to the severity of the asthmatic exacerbation, an individual experiences ventilation difficulties with various intensities of chest constriction, non-productive coughing, dyspnea, tachycardia, tachypnea and prolonged expiration with wheezing. Severe attacks also involve accessory respiration muscles, and wheezing is heard during inspiration and expiration. However, a typical individual is asymptomatic between exacerbations/attacks.

On the other hand, repeated attacks of refractory asthma (persistent symptoms despite high medication use) or poorly treated asthma can lead to abnormal pulmonary function tests even between attacks. Chronic airway inflammation also causes irreversible alterations known as airway remodeling [36]. They include airway smooth muscle hyperplasia and hypertrophy, aberrant accumulation of extracellular matrix (ECM), infiltration of inflammatory cells and goblet cell hyperplasia with augmented mucus secretion [37]. Further, elastic recoil is diminished due to an altered transmission between the lung parenchyma and the affected airways [17]. ECM composition is also altered in asthma. Interestingly, the ECM composition differs between corticosteroid-susceptible (controlled) asthma and corticosteroid-resistant (persistent) asthma.

Mechanisms controlling the pathogenesis of airway remodeling are poorly understood. One such mechanism is the extracellular matrix (ECM) production imbalance and collagen degradation. Matrix metalloproteinases (MMPs) are proteolytic enzymes playing central roles in the turnover [38].

### 3.3 Phenotypes in asthma

There are many phenotypes in asthma. Allergic asthma usually starts in childhood and is accompanied by other allergic diseases such as eczema, allergic rhinitis or food allergy. The patients often respond well to therapy and have a mild-to-moderate course. Specific IgE in the serum is a crucial feature of allergic asthma called atopic one. Blood and sputum eosinophils are usually elevated, and atopic dermatitis is frequently associated with this phenotype of asthma. Unlike allergic asthma, non-allergic asthma is rather associated with an absence of specific IgE in the serum. The patients usually require high doses of inhaled corticosteroids to control the disease. Their sputum samples contain neutrophils or eosinophils or low numbers of inflammatory cells. Besides allergic and non-allergic phenotypes, other phenotypes have been observed in asthma [36].

### 3.4 The current research in asthma

Asthmatic therapy targets the main immuno-pathophysiological mechanisms that were described above. The first line of asthma therapy is inhaled corticosteroids that decrease mucus production, swelling and Th2 immune response and several infiltrated immune cells in airways. The inhaled corticosteroids can be combined with long-acting beta-agonists (LABAs) or leukotriene modifiers. LABA stimulates beta-adrenergic receptors on smooth muscles of the airways, leading to their relaxation. Leukotrienes are products of arachidonic acid and contribute to Th2 immune response. Another add-on therapy option is long-acting muscarinic agents (LAMAs) that decrease bronchoconstriction by blocking acetylcholine.

A current review by Gans et al. summarises various therapeutic approaches that are already approved or under development [36]. Briefly, Omalizumab is a monoclonal antibody against IgE. The blocked IgE cannot then bind to its receptor on mast cells, not resulting in degranulation. Other two approved therapies block either IL-4R on T cells or IL-5R on eosinophils. Other drugs are currently tested *in vitro*, in mice, phase 1 and 2 clinical studies [39].

## 4. Sarcoidosis

### 4.1 Definition

Sarcoidosis is a granulomatous inflammatory disease affecting the lung in more than 90% of cases. Besides the pulmonary involvement, sarcoidosis can attack any organ, including the lymphoid system (both intrathoracic and extrathoracic lymph nodes), skin, oculars, heart, bone marrow, liver, kidney or nervous system in the order from the most frequently observed approximately [40, 41]. A new investigation has been concentrated on cardiac sarcoidosis [42]. In this text, however, I primarily focus on the pulmonary sarcoidosis.

The first clinical manifestation of pulmonary sarcoidosis relatively frequently shows a group of acute symptoms known as Löfgen's syndrome, a benign and self-remitting disease [43]. Nonetheless, sarcoidosis without the acute onset usually progresses as a chronic form in many patients who are thus treated with immunosuppressive drugs. The most severe cases (up to 20%) develop fibrotic pulmonary sarcoidosis (see **Table 2**), associated with the need for lung transplantation and a high mortality rate [44, 45].

The diagnostic criteria of sarcoidosis are defined in American Thoracic Society/the European Respiratory Society/the World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) International Consensus Statement [46]. The key diagnostic tool is chest roentgenograms or computed tomograms, which should be histologically confirmed by the presence of noncaseating epithelioid cell granulomas with no evidence of mycobacterial or fungal infections. Pulmonary function test (PFT) and diffuse capacity of carbon monoxide (DLCO) are applied to assess the improvement or deterioration of lung disease. The bronchoalveolar CD4+/CD8+ cell ratio is another clinical marker that is indicative for diagnostic purposes [41, 47]. Though some promising diagnostic biomarkers (e.g. serum angiotensin-converting enzyme) for sarcoidosis have been studied, we need someone with sufficient reliability.

| Stage | Finding |
|---|---|
| 0 | Normal chest radiograph |
| I | Bilateral hilar lymphadenopathy (BHL) |
| II | BHL plus pulmonary infiltrations |
| III | Pulmonary infiltrations (without BHL) |
| IV | Pulmonary fibrosis |

**Table 2.**
*Chest radiographic staging in pulmonary sarcoidosis.*

### 4.2 Pathophysiology of pulmonary sarcoidosis

A pathological hallmark is the presence of small, well-formed and compact areas of accumulated inflammatory cells called sarcoid granulomas in the affected organs. Regarding pulmonary sarcoidosis, the granuloma usually appears on the wall of the alveoli or bronchioles in the upper lobes of the lung. Besides this, they frequently occur in the hilar and mediastinal lymph nodes causing them to enlarge. The generally accepted hypothesis states that the formation of the sarcoid granulomas results from a response to so far unknown foreign antigen/pathogen. It is supported by other granulomatous diseases with known aetiological agents, such as tuberculosis, chronic beryllium diseases or occupational diseases [48–50].

The sarcoid granuloma belongs to immune non-necrotizing granulomas. It has a central follicle that is composed of multinucleated giant cells and activated T cells. The multinucleated giant cells are highly differentiated variants of macrophages that are formed from several macrophages fused with each other [2]. In an immunological model, they are likely formed when individual macrophages fail to eradicate persistent pathogens. Their formation does not necessarily correlate with their increased function. The multinucleated cells express MHC and also interact with T cells. In line with this model, CD4+ T lymphocytes are accumulated in the central sarcoid follicle. The central follicle is surrounded by the peripheral area composed of other T lymphocytes (CD4+ and CD8+), B lymphocytes, monocytes, mast cells and fibroblasts. The whole granulomas can be surrounded by lamellar rings of hyaline collagen [51].

The sarcoid granuloma is positive for angiotensin-converting enzyme (ACE) and amyloid A (AA). Both ACE and AA serum concentrations are up-regulated in sarcoidosis [52]. Immunological abnormalities further involve the intra-alveolar and interstitial accumulation of the CD4+ cells with T helper (Th) 1 and 17 cytokine profile [44]. In particular, in situ, elevations involves interleukin (IL)-2, IL-17, interferon-gamma (IFN-γ) and monocyte-recruiting chemokines. The accumulated alveolar macrophages are an important source of tumour necrosis factor-alpha (TNF-α), IL-1 and proteolytic enzymes in sarcoidosis.

The above-described inflammation chronically affects lung parenchyma, of which involvement is shown by decreased lung compliance. The decreased diffuse capacity (DLCO) is associated with alveolitis and vasculitis in sarcoidosis. Both parameters are more sensitive than lung volumes in detecting functional abnormalities [11]. In an advanced sarcoidosis course, an extensive fibrotic process secondary to the sarcoid granuloma deteriorates pulmonary function toward the PFT restrictive pattern with low total lung capacity (TLC) (the classic pattern of restriction). Some patients can have mild airway obstruction defined by low FEV1/FVC if parenchymal involvement extends to the airways.

### 4.3 Phenotypes in pulmonary sarcoidosis

We recognize two clinical phenotypes; Löfgen's syndrome and non-Löfgen's syndrome. Patients with the acute form, known as Löfgen's syndrome, are characterized by erythema nodosum, fever, bilateral hilar lymphadenopathy and polyarthralgia. Erythema nodosum is a clinically significant and easily recognizable skin lesion with raised, red, tender bumps or nodules on the legs. Adjacent joints are usually swollen and painful [53]. **Table 2** shows another classification that is based on radiographic imaging [46].

### 4.4 The current research in pulmonary sarcoidosis

The risk of development of pulmonary sarcoidosis is well-established to be associated with the genetic polymorphisms of human leukocyte antigen (HLA). For instance, the main results in the study by Rivera et al. confirmed several early published observations on genetic risk factors for sarcoidosis, e.g. HLA-DRB1*03, -DRB1*15, -DRB1*01 and others. The new contribution of this study is that these genetic factors and even new ones were ascribed to the sarcoid phenotypes; Löfgren's syndrome and non-Löfgren's syndrome. Generally, a higher presence of human leukocyte antigen (HLA) genes was reported in Löfgren's syndrome, whereas non-HLA genes were present in non-Löfgren's syndrome [54].

However, much research has yet to untangle the genetic background associated with particular phenotypes, mainly those with poor prognoses, such as the most advanced stage, sarcoidosis-associated fibrosis. The new investigation on fibrotic pulmonary sarcoidosis could also contribute to a better understanding pathophysiology in other idiopathic diseases with similar fibrotic processes.

## 5. Conclusion

At each breath-in, the respiratory system delivers oxygen to the body and its immune component protects the lungs against air born infection and pollution. If this protection is damaged, it strongly impacts lung function and the quality of our lives. Exposure to air born pollution and allergens leads to two common obstructive pulmonary diseases; COPD and asthma. COPD is the world's third leading cause of death. The number of patients with asthma is increasing in developed countries. Understanding the pathophysiology of these diseases is the first step in prevention and treatment. Many diagnostic and therapeutic tools are available at present.

Though a good efficacy of the current treatment in a typical patient, many patients do not benefit. A personal approach is highlighted to consider the heterogeneous character of asthma and various phenotypes in COPD. Genetic background is the subject of an intensive investigation in genome-wide association studies and whole genome sequencing. New prognostic and therapeutic biomarkers are studied to predict future development and provide more effective treatment without side-effect.

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