REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Inflammation in COPD: pathogenesis, local and systemic effects

CORNELIA BARBU, MIHAELA IORDACHE, M. G. MAN

Arges County Hospital, Pitesti

Abstract

COPD is a disease characterized by inflammation both in its stable phase and during exacerbations. Inflammation is present in the respiratory compartment, the inflammatory cells and different mediators of inflammation being present. Studies have shown that some mediators of inflammation have a high level at systemic level also, inducing a certain grade of systemic inflammation, mainly responsible for the systemic manifestation of the disease. It seems that the both local and the systemic inflammation are amplified during exacerbations. The purpose of this paper is to review the respiratory inflammatory reaction, to identify the main actors involved in the stable phase of the disease and during exacerbations, the systemic inflammation accompanying the local inflammation, and to find the possible interrelations between the systemic and local inflammation, on one hand, and the respiratory and extra-respiratory manifestations of COPD on the other hand. The understanding of the pathogenic mechanisms, which stay at the base of inflammation and of the possible interrelations shown, represents a theoretical interest and also a practical one, concerning the targets of different therapeutic agents which could be used in the management and in the control of the disease.

Keywords: COPD, local inflammation, systemic inflammation, systemic manifestations.

Introduction

Over the years, there were several attempts to define COPD, different from country to country, from decade to decade.

From this reason, in 2006, *The Global Initiative for Chronic Obstructive Pulmonary Disease* (*GOLD*) defined COPD as a pathologic state characterized by airflow limitation, which is not fully reversible. COPD comprises the pulmonary emphysema (condition anatomically defined by obstruction and enlargement of the pulmonary alveoli), the chronic bronchitis (which has a clinical definition, being characterized by chronic cough and expectoration) and the disease of small airways (pathologic condition that involves the small bronchioles) [1].

GOLD also mentions that COPD is "a preventable and treatable disease with some significant extra pulmonary effects. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" [2].

The risk factors involved in COPD are: smoking, reactivity of airways (at certain patients being increased, similar to patients with asthma), respiratory infections, professional factors (recognized at the miners who work with coal, gold and also at the workers in textile industry), atmospheric pollution, passive smoking [1].

The pulmonary emphysema is anatomically defined, by enlargement and destruction of the pulmonary structures involved in gaseous exchanges. The acinus is the structural unity distal to a terminal bronchiole, including three to five orders of respiratory bronchioles, alveolar ducts and alveolar sacs. The cetrolobular (centroacinar) emphysema is associated to affecting of the respiratory bronchioles and so to affecting of the central portion of the acinus. The panlobular (panacinar) emphysema affects the whole anatomic structure which is responsible with the gaseous exchanges.

The chronic bronchitis is clinically defined as a pathologic state characterized by cough with expectoration, for at least three consecutive months per year, for at least two years. Pathologically, the characteristic feature of chronic bronchitis is the hypertrophy and hyperplasia of submucosal glands mainly situated in the proximal airways. It was found also an increase of the number of the mucus-secreting goblet cells in the distal airways. The airways contain a rich inflammatory infiltrate and areas in which the normal ciliated respiratory epithelium is replaced by squamous epithelium. Small airways disease is pathologically characterized by distortions, tortuosities, fibrosis and smooth muscle hyperplasia of the small airways. There is a category of patients in which the airways obstruction is due to the bronchiolitis [2].

The chronic inflammation of the airways leads to obstruction (measured by spirometric by reduction of FEV1), which is not completely reversible at the bronchodilator tests. The chronic inflammation in COPD is due to amplification of the normal inflammatory response of the airways to chronic irritants, the most important being smoke. The mechanism responsible for this amplification is not fully known; is it possible to be genetically determined. At the smoker patients with COPD, we recognize three conditions of the airways, which can contribute to the relatively fixed limitation of the airflow. The first of them, the chronic bronchitis, is characterized by the inflammation of the airways wall, associated with the hyperplasia of the goblet cells, the enlargement of the tracheobronchic submucosa and the

mucous hypersecretion. The second, found in small airways disease, is characterized by an early change, which is the macrophage bronchiolitis, with an accumulation of both / CD8+ T-cells and the B-lymphocytes in the airways of about 2 mm or less in diameter. The mucous metaplasia and the hyperplasia, increased intraluminal mucus, the hypertrophia of bronchiolar wall muscle, the fibrosis, the stenoses of the small airways, and the loss of the elastic recoil represent essential histopathological conditions. The third, the microscopic and macroscopic emphysema, leading to the elastolytic destruction of the alveolar wall, is a major condition for the irreversible deterioration of the airflow [3].

Inflammation is responsible for the exacerbations in COPD, characterized by cellular activation, cytokines production, the cellular interactions, the tissue injury produced by inflammation mediators and also by the relationship with the symptoms of the disease during exacerbations [4].

The cells and the mediators involved in the amplified inflammatory response are responsible for the local effects but also for the systemic effects of the inflammation, described bellow.

The inflammatory reaction and the cells involved in inflammation

The studies published by now have shown that the structural anomalies, which define COPD, are associated with the inflammatory reaction of the airflow, alveoli and pulmonary vessels [5].

The main cells involved in inflammation are: neutrophils, eosinophils, lymphocytes and macrophages.

Neutrophils

The bronchial biopsies have shown the increase or neutrophils number in the bronchial glands, submucosa and subepitelial tissue in the stable phase of COPD, compared with the healthy subjects. The number of neutrophils seems to be positively related to the severity of airflow limitation, probably resulting from the bacterial colonization of the bronchia in severe obstruction forms of disease. During exacerbations, the number of neutrophils in submucosa and subepitelial tissue is greater compared with the stable phase of COPD, the increased number of neutrophils being positively related to the massive bronchial bacterial colonization, so as in the stable phase of the disease. White AJ *et al.* (2003) found that in the resolution phase of exacerbations, the decrease of neutrophil number in the bronchial structures is associated with the eradication of the bacteria in sputum [6]. Wetzler LM (2003) [7] and Ritter M *et al.* (2005) [8] suggest that the possible mechanism of neutrophilia in the bacterial infections might be the interaction of bacteria with the Toll-like receptors on the antigen presenting cells and epithelial cells.

The strongest chemo-attractant factors for neutrophils are considered to be: interleukin-8 (IL-8), leukotriene B4 (increased in exacerbations, so as leukotriene E4), epithelial cell-derived neutrophil attractant-78, and tumoral necrosis factor – α (TNF-α) [4].

The neutrophils have a major antibacterial role; they destroy the bacteria and at the same time, the neutrophils degranulate, leading to the myeloperoxidase releasing, a very strong oxidant agent.

Papi A *et al.* (2006) show that the increased number of neutrophils in sputum could be associated with the viral infection also, but could be present, at the same time, in the absence of any bacterial or viral infection [9].

Eosinophils

The eosinophilic inflammation is specific for asthma, but there is a certain phenotype of COPD characterized by little emphysema and thickening on computed tomography examination, and a good response to corticosteroids; in this type of COPD, in the stable phase of the disease, eosinophils seems to have an important role in developing inflammation [10, 11]. This phenotype of COPD has many asthma-like features.

During exacerbations of COPD, an asthma-like inflammatory infiltrate is observed, with numerous eosinophils [12]. The increased number of eosinophils in COPD exacerbations is due, at least partially, to viral infections. Hewson CA *et al.* (2005) [13] and Ritter M *et al.* (2005) [8] show that viruses are recognized by the Toll-like receptors on the epithelial cells, leading to some pro-inflammatory cytokines releasing. Therefore, during asthma exacerbations, the eosinophil attracting chemokines Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES), eotaxin, and interleukin-5 (IL-5) were found increased [3]. During exacerbations, we can also observe in sputum and in serum, the increasing products of eosinophils: eosinophilic cationic cationic protein, which causes tissue damage and remodeling *in vitro* studies [14]. This phenomenon could explain why the severe exacerbations leads to the pulmonary function decline [4].

Lymphocytes

Lymphocytes seem to play an important part in COPD appearance and progression.

In the stable phase of COPD, the CD8+ lymphocytes are increased in airways submucosa and in peripheral blood, the number of these cells being associated with the severity of airflow limitation. These cells have cytotoxic memory, born at the same time with the first airways infection, followed by a faster and increased response to the next infections. The CD8+ cells number remains increased in the airways several months after the viral infection and seems to become stable after six months [15].

The CD4+ lymphocytes, helper cells that produce the pro-inflammatory cytokines, are increased in the peripheral blood of the patients with COPD. Majori M *et al.* have shown that especially the number or γ-interferon producing cells is increased [16].

In the stable phase of COPD, the B-lymphocytes are also increased, playing an important part in the humoral immunity, at the level of bronchial and bronchiolar wall. About the pathogenic importance of CD4+ cells, several theories were suggested, such as the increase number of these cells by the viral infection [17] and a possible

autoimmune response, a reaction with smoke components or with the extracell matrix products [18].

During exacerbations, the lymphocytes number increases even more, both in sputum and on bronchial biopsies, which is not surprising, because of the well known importance of these cells in viruses clearing.

However, we know very few about the lymphocyte subpopulations involved, mechanisms responsible for their increased influx and their activity state [4].

Macrophages

Macrophages are increased in the bronchial tissue in the stable phase of COPD, compared to patients with chronic bronchitis or healthy subjects. The increased number of macrophages is induced by smoking; an increased number of macrophages is observed in airways submucosa of smokers, while stopping smoking leads to the decrease of the number of macrophages at asymptomatic smoker subjects [19, 20]. During COPD exacerbations, a relative or absolute increase of macrophages number was not found in sputum or on bronchial biopsies (possible because of abstinence from smoking in patients during exacerbations); however, because of the lack of large studies, we cannot decide that macrophages are not involved in exacerbations) [4].

A scheme of the inflammatory process in COPD shows that the events could follow this course: macrophages control the lower airspace; the component of cigarette smoke comes into contact with activated lung epithelial cells and with the alveolar macrophages, leading to cytokine and chemokine releasing (the neutrophil chemotactic cytokine IL-8, TNF-α, interleukin-1β). The next step is acute neutrophil recruitment and subacute accumulation of macrophages in the respiratory bronchioles and alveolar spaces. The CD8+ and CD4+ lymphocytes and probably other inflammatory and immune cells are attracted in the lower airspace. Concomitant smoking induced loss of cilia in the airway epithelium, which predisposes to bacterial infection with neutrophils. Long after smoking cease, an exuberant inflammatory response can be observed, suggesting that the mechanisms of cigarette smoke-induced inflammation initiating the disease differ from mechanisms sustaining inflammation after smoking cessation [1].

Systemic inflammation in COPD

The abnormal systemic inflammation in COPD was observed not only at pulmonary level, but also at systemic level. The serum biomarkers of inflammation such as different cytokines, adipokines, C-reactive protein (CRP) and certain coagulation factors, are increased during exacerbations. Many of systemic manifestations of COPD are the consequence of the inflammatory process. Thus, COPD might be considered a disease with organ specific manifestations and also with systemic manifestations [21].

In order to explain the systemic effects of inflammation, several mechanisms were proposed: the systemic spread of inflammation mediators from pulmonary compartment, the inflammatory reaction to tissue hypoxia, the reaction induced by bacterial product lipopolysaccharide during exacerbations (Wouters EF, 2005) [22], cigarette smoking involvement, the pulmonary hyperinflation, the skeletal muscle dysfunction and bone marrow involvement [23].

The systemic spread of inflammation mediators is not sustained by all the studies published; Vernooy JH *et al.* have shown that there is not a correlation between the soluble TNF-α level and its receptors and also the level of IL-8 in induced-sputum on one hand and the level of the same factors in blood, on the other hand [24]. The lack of this correlation was also sustained by Hurst MR *et al.* [25].

Smoking induces a low-grade of systemic inflammation and epithelial dysfunction, being a risk factor for both COPD and cardiovascular diseases. It was shown that the former smokers have also a certain grade of systemic inflammation, which indicates, on one hand that cigarette smoke is not the only risk factor responsible for the systemic inflammation in COPD, and on the other hand that an autoimmune component could be involved in the COPD pathogenesis [23].

Regarding hyperinflation, Vassilakopoulos T *et al.* have shown that this phenomenon might stimulate the cytokine production at pulmonary level, which could contribute to the systemic inflammation [26].

The skeletal muscles and the bone marrow seems to be involved in systemic inflammation developed in COPD. Thus, Rabinovich RA *et al.* found that the systemic inflammation, expressed by the plasma level of TNF-α, increases after the muscular effort in COPD patients, but not in healthy subjects [27].

The bone marrow might be implicated in systemic inflammation, because at its level the inflammatory cells are produced, whose presence is stimulated by smoking and air pollution [28, 29].

Defining the origin of systemic inflammation, there must be taken into account the ageing process, accelerated by smoking and the inverse linear relationship between the C-reactive protein concentration and the FEV1 level), the former indicating that the systemic inflammation could be associated with the early alteration of pulmonary function [23].

Further, we will refer to the inflammation mediators and biomarkers, which seem to play an important part in COPD exacerbations and in systemic effects of inflammation.

Several studies have shown the association between COPD and a low-grade of systemic inflammation. A meta-analysis of these studies done by Gan WQ *et al.* has shown that patients with stable COPD have an increased number of leukocytes (some of them with an activated phenotype), a high level of CRP and of fibrinogen, of certain cytokines (IL-6), and of TNF-α [30]. The intensity of systemic inflammation rises during exacerbations. Besides COPD, a certain degree of systemic inflammation is associated with other chronic conditions such as normal ageing, chronic heart failure, obesity, and diabetes mellitus [23].

Over the years, there were attempts to find an association between different inflammation markers concentration or number of different cells involved in

inflammation, and COPD stage. However, a recent meta-analysis has shown that this association of the disease severity can be made only with the systemic concentration level of TNF-α and CRP.

Because it has been demonstrated that the level of systemic inflammation increased during exacerbations [31], studies aimed to observe the evolution of inflammation biomarkers level during exacerbations, and also the possible association between this level and the evolution and prognosis of exacerbations. During exacerbations, there were found several systemic effects related to inflammation; the acute phase proteins increase, the complement components involved, the variations in adipokines concentration, the endothelial dysfunction, and the variations of hemostasis mechanisms in coagulation's favor [21].

Several studies have shown that systemic inflammation is up-regulated during exacerbations. The markers whose blood concentration was found increased are: C-reactive protein, interleukin-8, TNF-α, leptin, endothelin-1, cationic eosinophilic protein, mieloperoxydase, fibrinogen, interleukin-6, α_1-antitripsine, leukotrienes E4 and B4. The serum concentration of interleukin-6 and CRP during exacerbations is positively correlated to the airways inflammation markers and seems to be higher during bacterial infections [21]. Interleukin-6 is the most important inductor of acute phase proteins synthesis in hepatocytes [3].

Hurst JR *et al.* have shown that there are 36 biomarkers able to confirm the presence of an exacerbation in COPD and which could predict also the severity of exacerbation; among them, CRP seems to be the most sensible [31]. The maintenance at a high level of CRP serum level during exacerbation remission indicates the incomplete resolution of symptoms and the recurrence of exacerbation [32].

Besides CRP, differences between the concentration during the stable state of the disease and the concentration during exacerbation were found only for the following biomarkers: interleukin-6, myeloid progenitor inhibitory factor (MPIF-1), pulmonary and activation-regulated chemokine (PARC), adiponectin (ACRP-30), and soluble intercellular adhesion molecule (sICAM).

C-reactive protein is not only an inflammation marker, but also a pathogenic factor of inflammation. It participates at non-specific phase of the biochemical response to the majority forms of tissue damage, infections, inflammations and malignant neoplasia. During this phase of response, a rapid up-regulation of certain proteins is observed, mainly in hepatocytes. Together with C-reactive protein other acute phase proteins are rapidly produced: proteinase inhibitors, the coagulation proteins, the complement and transport proteins [21]. CRP is produced mainly by hepatocytes, under the transcriptional control of interleukin-6. The plasma half-time of CRP is the same for the healthy subjects and the ill patients, so its serum concentration indicates the intensity of CRP synthesis, which thus directly reflects the intensity of the pathologic process which stimulated CRP production.

The human CRP has a high affinity to phosphorcholine residues binding (universal factors present in eukaryocytes and also to other autologous constituents (plasma native or modified lipoproteins, damaged cell membranes, several phospholipids or related compounds, small nuclear ribonucleoprotein particles, apoptotic cells) or extrinsic (glycans, phospholipids, other constituents of microorganisms, such as capsular and somatic components of bacteria, fungi and parasites, as well as plant products) [33].

When the aggregation or binding to ligand macromolecules is done, the human CRP is recognized by C1q and thus the classical pathway of complement is activated. C1q is a member of the protein family classified as defense collagens. C1q is also a pattern recognition molecule, which can trigger rapid enhanced phagocytosis, leading to rapid clearance of cellular detritus, apoptotic cells and immune complexes. The complement system is a powerful effector mechanism, which, upon activation, generates activation fragments (C3a and C5a), resulting in initiation of a local inflammatory response by recruitment of leukocytes to the area of infection or injury [23].

Few studies show the complement system participation to the inflammatory reaction in COPD. Some of them have demonstrated an increase of C5a level in induced sputum of COPD patients, which is negative, correlated to the diffusion capacity [34].

In summary, CRP is involved in COPD pathogenesis, through the complement system. Another hypothesis is that which affirms the direct participation of CRP in the pathogenesis of airways inflammation, this former mechanism being demonstrated in the sputum of patients with airways inflammation, but not yet in patients with COPD [21].

Concerning participation of fat tissue in COPD pathogenesis, we know today that fat tissue produces several hormones and some proteic factors named adipokines or adipocytokines. Adipocytes secrete proteins, which are involved in lipid metabolism, insulin sensitivity, the alternative system of complement, the vascular homeostasia, the arterial blood pressure and angiogenesis and also in energetic balance regulation [21]. Among these substances produced in fat tissue, adiponectin and leptin were associated to the inflammatory process and with the immune response in COPD, both its stable form and its exacerbations [35].

Leptin is a peptidic hormone produced mainly in the fat tissue, its circulating form being proportional to the fat tissue quantity in any given subject. Its effects on the energy metabolism are exerted by the hypothalamic nuclei. Leptin is also involved in lipid and glucose metabolism, synthesis of glucocorticoids and insulin, regulation of the hypothalamic–pituitary–adrenal axis, maturation of the reproductive system, hematopoiesis, angiogenesis and fetal development [21].

During COPD exacerbations, variation of leptin level were observed, related to variations of the energy metabolism and systemic inflammatory response [36].

Several studies demonstrated that leptin could play a major pro-inflammatory part acting like a cytokine, being involved in inflammation and autoimmune diseases pathogenesis and thus, being able to interfere in acute exacerbations of COPD. Leptin could interfere in

immune processes (stimulating neutrophil and macrophage chemo-attraction, increasing the functions of these cells such as oxidative capacity, phagocytosis and cytokine secretion, activating and increasing the proliferating effects on T-lymphocytes and promoting Th1-cell differentiation). Leptin also enhances host responses to inflammation and infection by stimulating tissue repair due to its mitogenic and angiogenic effects on epithelium and endothelium [21].

If leptin has proinflammatory effects, it was shown that adiponectin has anti-inflammatory properties. Adiponectin has an important role in regulation of insulin sensitivity and it has a molecule composed of a globular and a collagenous domain. The globular domain of adiponectin has close structural similarities with TNF-α. Leukocyte elastase could cleave the adiponectin molecule and release this globular domain, thus activated leukocytes could interfere in adiponectin bioactivity. Adiponectin reduces TNF-α production and also its activity, inhibits IL-6 production and induces the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist, as shown in studies with animal and human models [37, 38]. These effects could be explained by nuclear factor (NF)-κB inhibition by adiponectin. Furthermore, adiponectin reduces induction of the endothelial adhesion molecules ICAM-1 and vascular cell adhesion molecule-1 [21].

Considering all these pro-inflammatory/anti-inflammatory effects of leptin and adiponectin, we can conclude that obesity, per se, induces a low-grade of systemic inflammation. Thus, we can consider that obesity could amplify the inflammation in COPD exacerbations in obese patients, but this is a hypothesis that must be demonstrated.

The vascular endothelium produces vaso-relaxing and vaso-constrictive substances.

An imbalance between these two categories of substances could explain the endothelial dysfunction. Several biomarkers were associated both COPD and endothelial dysfunction, such as: CRP, fibrinogen and serum complement, ICAM-1, IL-6, TNF-α, endothelin-1 and leptin, the first three being the most important [21].

During exacerbations, the CRP level is high. CRP down-regulates the endothelial nitric oxide synthase (eNOS), up-regulates adhesion molecules, stimulates MCP-1 while facilitating macrophage low-density lipoprotein uptake, facilitates endothelial cell apoptosis, inhibit angiogenesis, up-regulates NF-κB, having a proatherogenic effect. In the vascular smooth muscle, it up-regulates angiotensin type 1 receptors and stimulates vascular smooth muscle migration, proliferation, neointimal formation and reactive oxygen species production [39]. Furthermore, CRP directly inhibits endothelial progenitor cell differentiation, survival and function, properties that associate inflammation to cardiovascular diseases. CRP also increases plasma fibrinogen level during COPD exacerbations, promoting the cardiovascular diseases in COPD patients [21].

Leptin has also proatherogenic properties; it induces the endothelial dysfunction, stimulates the inflammatory reactions, oxidative stress, decreases the paraoxonase activity, playing an important role in oxidative modification of plasma lipoproteins, platelet aggregation, migration, hypertrophy and proliferation of vascular smooth muscle [40].

The endothelial cells secret several components of complement, process regulated by cytokines add affected by pro-inflammatory stimuli, such as hypoxia (present in COPD), and tissue reoxygenation. Stimulation by complement activation products leads to a pro-inflammatory and coagulation state of endothelial cells, involved in cardiovascular pathology [21].

A prothrombotic state was observed in COPD; a high rate of platelet aggregation, promoted by hypercapnia and/or hypoxemia [41], an increased platelets, activation [42]. Compared to healthy subjects, patients with COP have a significantly high level of certain coagulation markers, such as thrombin-antithrombin III complex (TAT), fibrinopeptide A, plasminogen activator inhibitor type 1 (PAI-1). Concerning the coagulation/fibrinolysis balance, in COPD it is observed that inflammation shifts this balance to coagulation favor. Fibrinogen has a high level in patients with both stable COPD and exacerbations. Coagulation promoted by inflammatory mechanisms is due mainly to the induction of tissue factor expression on the cell surface of leukocytes, particularly monocytes. Also, CRP, whose level is high, could facilitate the monocytes-endothelial cells interaction, and thus promotes PAI-1 and tissue factor. The platelet production is increased by inflammation mediators, such as IL-6. The inflammation mediators can indirectly increase the platelet activity, by inducing the expression of protease-activated receptors on the endothelium. In inflammation presence, the inhibitory activity of antithrombin is decreased, which leads to delayed inhibition of the coagulation enzymes that favor intravascular coagulation. Concerning the anticoagulant mechanisms, the protein C pathway appears to be especially sensitive to down-regulation by anti-inflammatory mediators. On the other hand, once control of thrombin and other coagulation enzymes is lost, they can promote the inflammatory response [21]. Thus, platelets contain and release high concentrations of proinflammatory mediator CD4) ligand, which induce tissue factor synthesis and increases inflammatory cytokines, such as IL-6 and IL-8. Thrombin is involved in several humoral and cellular responses of inflammation and also in cell proliferation [43]. Tissue-factor VIIa complex can activate protease activated receptors, leading to increased expression of adhesion molecules which facilitate leukocyte-mediated vessel injury' fibrin also can participate in regulation of different mechanisms of inflammation [21].

Systemic manifestation of COPD

Today, COPD is considered a systemic disease, inflammation mediators being mainly responsible for COPD systemic manifestations. These mediators induce a catabolic state, which leads to weight loss, muscle weakness, and changes in peripheral muscle metabolism. In these effects there is also involved a certain anabolic hormones decrease, such as androgens [2].

Among the mediators of systemic inflammation, cytokines, especially TNF-α, activate nuclear factor NF-κB, transcription, up-regulate the inducible form of the nitric oxide synthesis, and facilitate the degradation of myosin heavy chains through ubiquitin-proteasome complex, promote apoptosis in skeleton muscle [23].

Tobacco smoking is a major risk factor for both COPD and cardiovascular diseases. However, the cardiovascular risk is higher in smokers with COPD compared to smokers without COPD. COPD is also associated with the increased incidence of depression, osteoporosis and lung cancer [23]. The understanding of pathogenic mechanisms, which could explain these associations, needs future studies.

COPD is closely associated with inflammation, both in the stable phase of the disease and during exacerbations. Local inflammation, in the broncho-alveolar compartment, is associated with a certain degree of systemic inflammation. The inflammation mediators are involved in the appearance of local, respiratory histopathological changes, and also explain many of systemic manifestations of COPD. The relationship between local inflammation, systemic inflammation and pathological mechanisms, which are responsible for the respiratory and extrarespiratory manifestations of the disease induced by inflammation remains to be clarified by future studies.

References

[1] Reilly JJ, Silverman EK, Shapiro SD, Chronic obstructive pulmonary disease. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL (eds), *Harrison's principles of internal medicine*, 16th edition, McGraw–Hill Professional, 2004, 1547–1560.

[2] MacNee W, ZuWallack RL, Keenan J, *Clinical management of chronic obstructive pulmonary disease*, 2nd edition, Professional Communications, New York, 2005.

[3] Jeffery PK, Pathology of asthma compared with chronic obstructive pulmonary disease. In: Adkinson F, Busse WW, Bochner BS, Holgate ST, Simons FER, Lemanske RF (eds), *Middleton's allergy: principles and practice*, 7th edition, Mosby, 2009, 921–936.

[4] Bathoorn E, Kerstjens H, Postma D, Timens W, MacNee W, *Airways inflammation and treatment during acute exacerbations of COPD*, Int J Chron Obstruct Pulmon Dis, 2008, 3(2):217–229.

[5] Barnes PJ, Shapiro SD, Pauwels RA, *Chronic obstructive pulmonary disease: molecular and cellular mechanisms*, Eur Respir J, 2003, 22(4):672–688.

[6] White AJ, Gompertz S, Bayley DL, Hill SL, O'Brien C, Unsal I, Stockley RA, *Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis*, Thorax, 2003, 58(8):680–685.

[7] Wetzler LM, *The role of Toll-like receptor 2 in microbial disease and immunity*, Vaccine, 2003, 21(Suppl 2):S55–S60.

[8] Ritter M, Mennerich D, Weith A, Seither P, *Characterization of Toll-like receptors in primary lung epithelial cells: strong impact of the TLR3 ligand poly(I:C) on regulation of Toll-like receptors, adaptor proteins and inflammatory response*, J Inflamm (Lond), 2005, 2:16.

[9] Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL, *Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations*, Am J Respir Crit Care Med, 2006, 173(10):1114–1121.

[10] Kitaguchi Y, Fujimoto K, Kubo K, Honda T, *Characteristics of COPD phenotypes classified according to the findings of HRCT*, Respir Med, 2006, 100(10):1742–1752.

[11] Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, Pavord ID, *Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial*, Lancet, 2000, 356(9240):1480–1485.

[12] Barnes PJ, *Chronic obstructive pulmonary disease*, N Engl J Med, 2000, 343(4):269–280.

[13] Hewson CA, Jardine A, Edwards MR, Laza-Stanca V, Johnston SL, *Toll-like receptor 3 is induced by and mediates antiviral activity against rhinovirus infection of human bronchial epithelial cells*, J Virol, 2005, 79(19):12273–12279.

[14] Zagai U, Sköld CM, Trulson A, Venge P, Lundahl J, *The effect of eosinophils on collagen gel contraction and implications for tissue remodeling*, Clin Exp Immunol, 2004, 135(3):427–433.

[15] Hogan RJ, Usherwood WJ, Zhong W, Roberts AA, Dutton RW, Harmsen AG, Woodland DL, *Activated antigen-specific CD8+ T-cells persist in the lung following recovery from respiratory virus infection*, J Immunol, 2001, 166(3):1813–1822.

[16] Majori M, Corradi M, Caminati A, Cacciani G, Bertacco S, Pesci A, *Predominant TH1 cytokine pattern in peripheral blood from subjects with chronic obstructive pulmonary disease*, J Allergy Clin Immunol, 1999, 103(3 Pt 1):458–462.

[17] Majo J, Ghezzo H, Cossio MG, *Lymphocyte population and apoptosis in the lungs of smokers and their relation to emphysema*, Eur Respir J, 2001, 17(5):946–953.

[18] Agustí A, MacNee W, Donaldson K, Cosio M, *Hypothesis: does COPD have an autoimmune component?*, Thorax, 2003, 58(10):832–834.

[19] Willemse BWM, ten Hacken NHT, Rutgers B, Postma DS, Timens W, *Association of current smoking with airway inflammation in chronic obstructive pulmonary disease and asymptomatic smokers*, Respir Res, 2005, 6:38.

[20] Willemse BWM, ten Hacken NHT, Rutgers B, Lesman-Leegte IG, Postma DS, Timens W, *Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers*, Eur Respir J, 2005, 26(5):835–845.

[21] Wouters EFM, Groenewegen KH, Dentener MA, Vernooy JHJ, *Systemic inflammation in chronic obstructive pulmonary disease: the role of exacerbations*, Proc Am Thorac Soc, 2007, 4(8):626–634.

[22] Wouters EF, *Local and systemic inflammation in chronic obstructive pulmonary disease*, Proc Am Thorac Soc, 2005, 2(1):26–33.

[23] Agustí A, *Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should)*, Proc Am Thorac Soc, 2007, 4(7):522–525.

[24] Vernooy JH, Küçükaycan M, Jacobs JA, Chavannes NH, Buurman WA, Dentener MA, Wouters EF, *Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum*, Am J Respir Crit Care Med, 2002, 166(9):1218–1224.

[25] Hurst MR, Wilkinson TM, Perera WR, Donaldson GC, Wedzicha JA, *Relationships among bacteria, upper airway, lower airway, and systemic inflammation in COPD*, Chest, 2005, 127(4):1219–1226.

[26] Vassilakopoulos T, Roussos C, Zakynthinos S, *The immune response to resistive breathing*, Eur Respir J, 2004, 24(6):1033–1043.

[27] Rabinovich RA, Figueras M, Ardite E, Carbó N, Troosters T, Filella X, Barberà JA, Fernandez-Checa JC, Argilés JM, Roca J, *Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients*, Eur Respir J, 2003, 21(5):789–794.

[28] van Eeden SF, Hogg JC, *The response of human bone marrow to chronic cigarette smoking*, Eur Respir J, 2000, 15(5):915–921.

[29] van Eeden SF, Yeung A, Quinlam K, Hogg JC, *Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease*, Proc Am Thorac Soc, 2005, 2(1):61–67.

[30] Gan WQ, Man SF, Senthilselvan A, Sin DD, *Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis*, Thorax, 2004, 59(7):574–580.

[31] Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, Vessey RS, Wedzicha JA, *Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease*, Am J Respir Crit Care Med, 2006, 174(8):867–874.
[32] Perera WR, Hurst JR, Wilkinson TM, Sapsford RJ, Müllerova H, Donaldson GC, Wedzicha JA, *Inflammatory changes, recovery and recurrence at COPD exacerbation*, Eur Respir J, 2007, 29(3):527–534.
[33] Pepys MB, Hirschfield GM, *C-reactive protein: a critical update*, J Clin Invest, 2003, 111(12):1805–1812.
[34] Marc MM, Korosec P, Kosnik M, Kern I, Flezar M, Suskovic S, Sorli J, *Complement factors c3a, c4a and c5a in chronic obstructive pulmonary disease and asthma*, Am J Respir Cell Mol Biol, 2004, 31(2):216–219.
[35] Pinto-Plata VM, Livnat G, Girish M, Cabral H, Masdin P, Linacre P, Dew R, Kenney L, Celli BR, *Systematic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD*, Chest, 2007, 131(1):37–43.
[36] Creutzberg EC, Wouters EF, Vanderhoven-Augustin IM, Dentener MA, Schols AM, *Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease*, Am J Respir Crit Care Med, 2000, 162(4 Pt 1):1239–1245.
[37] Masaki T, Chiba S, Tatsukawa H, Yasuda T, Noguchi H, Seike M, Yoshimatsu H, *Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice*, Hepatology, 2004, 40(1):177–184.
[38] Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H, *Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes*, Biochem Biophys Res Commun, 2004, 323(2):630–635.
[39] Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, Li RK, Mickle DA, Verma S, *C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle*, Circulation, 2003, 107(13):1783–1790.
[40] Beltowski J, *Leptin and atherosclerosis*, Atherosclerosis, 2006, 189(1):47–60.
[41] Wedzicha JA, Syndercombe-Court D, Tan KC, *Increased platelet aggregate formation in patients with chronic airflow obstruction and hypoxaemia*, Thorax, 1991, 46(7):504–507.
[42] Ferroni P, Basili S, Martini F, Vieri M, Labbadia G, Cordova C, Alessandri C, Gazzaniga PP, *Soluble P-selectin as a marker of platelet hyperactivity in patients with chronic obstructive pulmonary disease*, J Investig Med, 2000, 48(1):21–27.
[43] Esmon CT, *The interaction between inflammation and coagulation*, Br J Haematol, 2005, 131(4):417–430.

Corresponding author
Cornelia Barbu, MD, PhD, Department of Internal Medicine, University of Piteşti, Argeş County Hospital, 36 Spitalului Alley, 110084 Piteşti, Romania; Phone +40248–287 150 / 297, +40722–547 584, Fax +40248–287 202, e-mail: barbucornelia@yahoo.com

Received: September 10th, 2010

Accepted: January 15th, 2011