Cross Current International Journal of Medical and Biosciences
Abbreviated Key Title: Cross Current Int J Med Biosci
ISSN: 2663-2446 (Print) & Open Access

Volume-2 | Issue-1 | Jan-2020 |

Review Article

Diagnosis of Chronic Obstructive Air Way Disease-Made Easy

Dr. Anil Batta
Professor & Head, Department of Medical Biochemistry, Govt.Medical College, Amritsar, Punjab, India

***Corresponding author:**
Dr. Anil Batta
Received: 21.12.2019
Accepted: 07.01.2020
Published: 23.01.2020

Abstract: Chronic obstructive pulmonary disease is an inflammatory disease. Together with oxidant stimuli, which directly affect lung structures, macrophages, neutrophils and CD8+ lymphocytes actively participate in the pathogenesis of the disease and promote biochemical reactions that result in progressive alteration of the upper airways and irreversible lung remodeling. The release of substances promoted by inflammatory cell recruitment and by oxidative stress lead to a temporary imbalance in the pulmonary defense mechanisms. Understanding the long-term maintenance of this imbalance is key to understanding the current physiopathology of the disease. The present study explores the cellular and molecular alterations seen in chronic obstructive pulmonary disease.

Keywords: Pulmonary disease, chronic obstructive/physiopathology; Lung/metabolism; Inflammation; Oxydants; Antioxidants; Oxidative stress.

INTRODUCTION

The prevalence of chronic obstructive pulmonary disease (COPD) has increased worldwide due to the ongoing exposure of people to well-known risk factors such as smoking, cadmium and silica (the last two being occupational hazards), as well as to higher pollution indices in open and closed environments. These factors, combined with the increased life expectancy of the population, led the World Health Organization to consider COPD to be an epidemic, which will predictably reach its peak by the year 2020, when it will likely become the third leading cause of mortality and the fifth most prevalent disease worldwide. With this negative perspective in mind, efforts are being made to avert this medical and economical catastrophe, since the current cost of treating COPD is already extremely high. Over the past years, various researchers explored new horizons in physiopathology, thereby changing the focus to the cellular and biochemical study of the disease. Until then, the focus was almost exclusively on pulmonary function. This concept was introduced in the definition of COPD by the Global Initiative for Chronic Obstructive Lung Disease (Pauwels, R. A. *et al.*, 2001). The characteristics of COPD are alterations in the cellular components of the lung (with an increased number of macrophages, neutrophils and CD8 lymphocytes), an excess of oxidative products and the facilitation of colonization by microorganisms (Barnes, P.J. 2000). Such factors interact in order to recruit more pro-inflammatory cells. The peripheral destruction of the alveolar attachments occurs in the areas of greater pulmonary ventilation, facilitating their fusion and hyperinflation (emphysema) (Barnes, P.J. 2000; & Barnes, P.J. 2003). The cells and biochemical components involved in the pathogenesis of COPD are herein described in detail.

INFLAMMATORY CELLS IN COPD

NEUTROPHILS

It is believed that this is due to the rapid migration of the neutrophils to the alveoli and the heterogeneity of the inflammatory process (Wagner, J.G., & Roth, R.A. 2000; & Jeffery, P.K. 1999). Another important factor is that neutrophils are approximately 8 μ in diameter, whereas the diameter of a pulmonary capillary is 5.5 μ. Therefore, a neutrophil has to be deformed in order to flow effectively through the blood stream. However, despite their size, neutrophils are most often seen in the pulmonary

Quick Response Code

Journal homepage:
https://crosscurrentpublisher.com/ccijmb/

DOI : 10.36344/ccijmb.2020.v02i01.001

capillary, showing a preference for this site in the vascular bed, and they occasionally remain in this region for a matter of minutes. When stimulated by certain substances, neutrophils stiffen and can no longer proceed through the circulatory system, being sequestered at the site (Wagner, J.G., & Roth, R.A. 2000; & Jeffery, P.K. 1999). Both the structure and the function of the neutrophils are modified in smokers. Smoking increases the number of cytoplasmic inclusions in some resident lung cells and alters the receptor fixation for the C3 component of the activated complement, which hinders phagocytosis. It also decreases neutrophil and macrophage membrane roughness (Dallegri, F. 1997). Protein substances, such as elastase, acid phosphatase, beta-glucuronidases, myeloperoxidase, metalloproteinases, lipocaine combined with gelatinase, proteinase 3 and cathepsin G, are released from the neutrophil granules. Such substances can participate, directly or indirectly, in the destruction of the lung parenchyma. Neutrophil apoptosis can be altered in COPD patients who use corticosteroids. In asthma, the eosinophil is one of the principal cells involved in the inflammatory process, and corticosteroids amplify apoptosis and increase the macrophagic depuration of eosinophils, decreasing the inflammatory process. In COPD, corticosteroids prolong neutrophil survival, maintaining the neutrophilic pulmonary process.

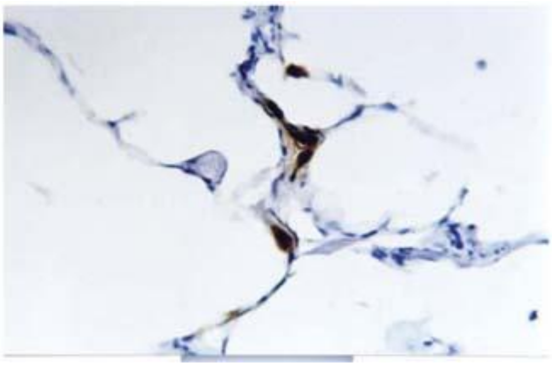

Fig-1. Staining of Cellular Subtypes CD8 T Lymphocytes in A Chronic Obstructive Pulmonary Biopsy

LYMPHOCYTES

Evidence accumulated over the past six years indicates that cytotoxic CD8 T lymphocytes play a significant role in the pathogenesis of COPD. The adaptive immune response is normally initiated in the child after vaccination or infection and depends preferably on the lymphocytes. The association and balance of the innate immunity provided by neutrophils, macrophages and natural killer cells, among others, together with that of adaptive immunity, strengthen the defense system against potentially pathogenic microorganisms and other antigens (Liu, C. C. *et al.*, 1996). All of the effects of T lymphocytes depend on the interaction with cells that contain specific proteins. The major histocompatibility complex (MHC) consists of glycoproteins of the cellular membrane binding to antigenic peptides, and they are divided into two classes: MHC I and II MHC (Liu, C. C. *et al.*, 1996). The CD8 lymphocytes are predominant in the perivascular regions, whereas the CD4 lymphocytes are predominant in the subepithelium. When the CD8 lymphocytes are activated, they cause the cytolysis of infected cells, or cells altered by their host, through the release of IFN-g and TNF-a, resulting in rapid resolution of viral infections. It has been demonstrated in experimental models that the excessive and inappropriate stimulation of CD8$^+$ causes destructive pathological pulmonary alterations (Figure 2) (e Silva, J. L. *et al.*, 1989).

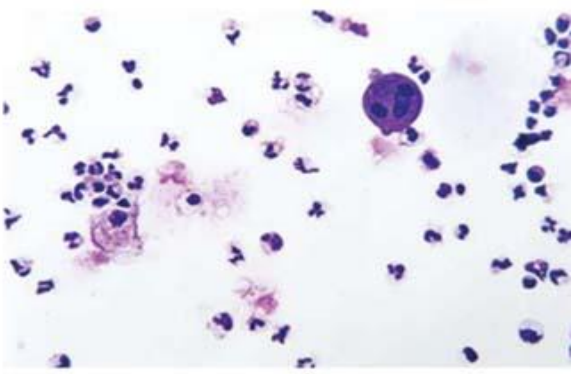

Fig-2. Neutrophilic induced sputum in chronic obstructive pulmonary disease

EOSINOPHILS

The role of the eosinophils in the pathogenesis of COPD is still controversial and open to speculation. Similarly to basophils, eosinophils develop from stem cells in the bone marrow. Eosinophils constitute one of the cells directly related to asthma. In COPD, some studies have identified eosinophils in exacerbations, as well as in the phases of stability of the disease, through biopsies, bronchoalveolar lavage and sputum analysis. Initially, it was believed that eosinophils were present only in a subtype of COPD, with clinicar behavior similar to asthma. However, various studies have identified eosinophils in COPD exacerbation (Figure 3).

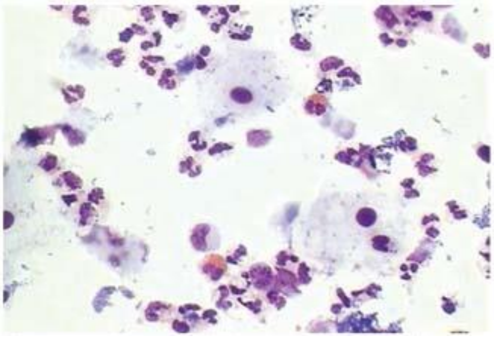

Fig-3. Patient with chronic obstructive air way disease without exacerbations for more than two months with eosinophils in induced sputum material

MACROPHAGES

Macrophages play an important role in the development of COPD and are found to be in increased numbers in the bronchial wall as well as in the lung parenchyma, especially in the alveolar spaces, in patients with COPD. Macrophages are cells derived from the bone marrow and the blood monocyte. They constitute the most common cell type among those that reside in the lung. They have various functions: they phagocyte particles or antigens; participate in the presentation of antigens to T lymphocytes; and can release various cytokines and active metabolites of arachidonic acid. They present significant pleomorphism in the lung, and different sizes. The smaller ones present intense phagocytosis capacity, and the larger ones exhibit great biochemical activity (Salamone, G. *et al.*, 2001).

In general, macrophages represent 90% of recovered cells in the cellular counts of the bronchoalveolar lavage. This percentage can even be maintained in smokers. However, the absolute number is usually four- to five-fold greater. They are diffusely located from the upper airways to the alveoli (Figure 4).

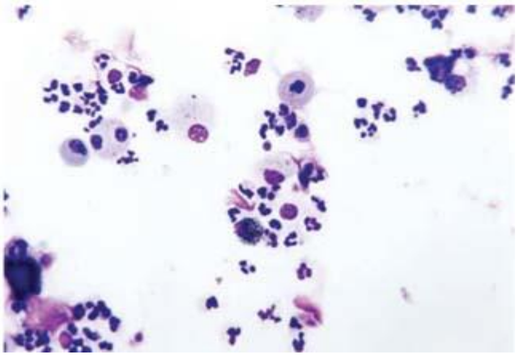

Fig-4. Macrophage predominance in the induced sputum of a patient with chronic obstructive pulmonary disease

In smokers, there is a greater release of lysosomes, up to five times more than in nonsmokers, secreting a variety of substances: metabolites of arachidonic acid: thromboxane E2, prostaglandin D2, prostaglandin F2a, leukotriene B4 and 5-hydroxyeicosatetraenoic acid; cytokines: IL-1, IL-6, TNF-a, IFN- a IFN-b, IL-10, IL-12, IL-15 and macrophage inhibitory factor; oxygen metabolites: superoxide anion (02-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH-); enzymes: metalloproteinases and elastases; and nitric oxide (Jeffery, P.K. 1999).

ROLE OF INFECTIONS

Viruses

Some authors(Haslett, C. 1999) have proposed that latent adenovirus infection in the airway mucosa of some individuals results in excessive recruitment of inflammatory cells exposed to smoking. Adenovirus increases the pro-inflammatory pathway of the nuclear factor B (NF- B), increasing the induction of intercellular adhesion molecule-1 and IL-8.

Other authors (Majo, J. *et al.*, 2001) formulated the hypothesis that viral infection induces greater expression of epithelial RANTES in patients with chronic bronchitis during the exacerbation phase. The most involved viruses are the rhinovirus, the respiratory syncytial virus, and the influenza virus. However, there might be bacteria as well.

Bacteria

The loss of cilia due to smoking can alter the mucociliary clearance response, principally of bacteria, and predispose the patient to colonization and recurrent infections, with high concentrations of proteinases, metalloproteinases and cytochemical mediators (IL-6 and IL-8), resulting in a persistent inflammatory process (Pauwels, R. A. *et al.*, 2001; & Wagner, J.G., & Roth, R.A. 2000).

CHART 1: P**rincipal antiproteases & proteases that participate in COPD**

ANTIPROTEASES	PROTEASES
α-1 ANTITRYPSIN	NEUTROPHIL ELASTASE PROTEINASE
α-2 MACROGLOBULIN	PROTEINASE 3 CATHEPSIN G
LEUCOPROTEASE INHIBITORS	METALLPROTEINASE
TIMP 1	METALLPROTEINASE
TIMP 2	CATHEPSIN S CYSTEINE PROTEINASE

PROTEASES AND ANTIPROTEASES

Proteinase Inhibitors

Primarily synthesized in the liver, 1-antitrypsin is a 52-kDa glycoprotein. It consists of a polypeptide chain of 394 amino acids and can inhibit the proteolytic activity of neutrophil elastase and other proteinases. In 1963, some authors (Pauwels, R. A. *et al.*, 2001; & Jeffery, P.K. 1999) proposed an association between 1-antitrypsin serum deficiency and emphysema, originating a theory that an imbalance between proteinases and antiproteinases sparks the genesis of COPD. Its genetic deficiency results in pulmonary emphysema in young nonsmokers (Chart 1).

Inhibitors of metalloproteinases

The tissue inhibitors of metalloproteinases (TIMP), four in all, are secreted by various cells and are present in the tissues in great concentrations. Macrophages secrete metalloproteinases, as well as TIMP-1 and TIMP-2. The TIMP-1 binds to the C-terminal of the metalloproteinases. The TIMP-2 interacts specifically with gelatinases A and B, with metalloproteinases 2 and 9, respectively (Barnes, P. J. *et al.*, 2004; & Liu, C. C. *et al.*, 1996).

Neutrophil proteinases

Neutrophil proteinases are a group of enzymes with distinct biological functions, including digestive enzymes of exocrine glands, coagulation factors and proteinases associated with leukocyte granules. The serine proteinases are synthesized as proenzymes in the endoplasmic reticulum (for example, in the azurophil granules) (Liu, C. C. *et al.*, 1996; & Saetta, M. *et al.*, 1998).

Neutrophil elastase

Neutrophil elastase acts against the proteins of the extracellular matrix, especially elastin. It is directly involved in the genesis of COPD. Various studies have demonstrated increased concentrations of neutrophil elastase in the bronchoalveolar lavage and sputum of smokers (e Silva, J. L. *et al.*, 1989).

Neutrophil cathepsin G

Neutrophil cathepsin G is stored in the neutrophil granules and, in lower concentrations, in the mastocytes and monocytes. In addition, it acts against elastin but destroys other proteins of the cellular matrix. It is related to facilitating penetration of the neutrophils into the bronchial endothelium and epithelium (Jeffery, P.K. 1999).

Neutrophil Metalloproteinase

Neutrophils contain two matrix metalloproteinases: gelatinase B and neutrophil collagenase. The collagenase degrades interstitial collagen. The gelatinase acts against gelatins, components of the basal membrane and elastin (Haslett, C. 1999).

Cysteine (thiol) proteinase of macrophage

The human alveolar macrophage produces lysosomal-thiol-proteinase and cathepsins B, H, L and S. These enzymes are very similar, with maximum activity at acid pH, and act in the pulmonary extracellular matrix. Cathepsin S has elastolytic activity (Salamone, G. *et al.*, 2001).

SUMMARY AND CONCLUSION

The respiratory tract is constantly exposed to oxidant effects. Oxygen, inhaled gases, oxygen peroxide, nitric oxide, sulfur dioxide and cigarette smoke have strong oxidant effects. During infectious pulmonary processes, granulocytes and macrophages form oxidants. These cells produce oxidants to destroy microorganisms. However, they also have a destructive effect on the tissue where they are located (Barnes, P.J. 2004; & Barnes, P.J. 2000). Tobacco contains over 1017 particles, many of which are oxidant products, including nitrogen oxides, organic free radicals and aldehydes (acrolein). Many inflammatory cells are recruited to the lung in response to cigarette smoke, and they also generate oxidant radicals. Antioxidants, such as superoxide dismutase, are also increased in smokers. Nevertheless, although this oxidant and antioxidant balance is altered in COPD, its real functional meaning has yet to be proven (Majo, J. *et al.*, 2001). The oxidation products can inactivate the a1-antitrypsin in vitro and the leukoprotease inhibitor. The reactive oxygen molecules (O_2-, H_2O_2, OH- and peroxynitrite) can increase mucous secretion and capillary permeability, resulting in bronchoconstriction. Oxidative stress can also increase the NF-kB transcription factor, resulting in increased IL-8 and TNF-a release and leading to greater neutrophil recruitment (O'Shaughnessy, T. C. *et al.*, 1997). The idea that emphysema results from proteolytic injury to alveolar septa has been the theory that best fits the knowledge acquired in recent years. The hypothesis of a protease-antiprotease imbalance has also been postulated, according to which an episodic or regular proteinase release occurs in the pulmonary tissue, digesting the proteins that sustain the pulmonary structure. The lung is normally protected by the effect of protease inhibitors, principally those coming from the blood. However, they can also be produced locally. Emphysema would result in a protease-antiprotease imbalance in favor of the proteases. The pulmonary repair would be insufficient and deficient, and functional changes would soon occur. It is evident that the risk factors already identified would be the principal determinants of the onset of the cellular inflammatory process and oxidative stress. When associated with a genetic predisposition, these risk factors would lead to a dysfunction of the inflammatory cells, such as the CD8 T lymphocytes and macrophages, which would remain activated in the pulmonary tissue, resulting in progressive destruction of the parenchyma and eventually in COPD . The metalloproteinases constitute a family of enzymes (more than twenty enzymes that degrade the pulmonary extracellular matrix). They are essential to the normal development of the pulmonary tissue, as well as to its remodeling and repair. Abnormal expressions have been found and related to the pulmonary destruction caused by COPD. They are secreted as pro-enzymes and activated on the surface of the cellular membrane or within the extracellular space, through the proteolytic cleavage of the N-terminal (Dallegri, F. 1997). The metalloproteinases can be classified as collagenases, gelatinases, stromelysins, matrilysins and metalloelastases.

REFERENCES

1. Barnes, P. J., Ito, K., & Adcock, I. M. (2004). Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase. *The Lancet*, *363*(9410), 731-733.
2. Barnes, P.J. (2000). Chronic obstructive pulmonary disease. N Engl J Med. 2000;343(4):269-80. Comment in: N Engl J Med. 2000;343(26):1969-70; author reply 1970-1; N Engl J Med. 2000;343(26):1970; author reply

1970-1;N Engl J Med. 2000;343(26):1970; author reply 1970-1.

3. Barnes, P.J. (2003). New concepts in chronic obstructive pulmonary disease. Annu Rev Med, 54, 113-29.
4. Barnes, P.J. (2004). Small airways in COPD. N Engl J Med. 2004;350(56):2635-7. Comment in: N Engl J Med. 2004;351(14):1459-61; author reply 1459-61. Comment on: N Engl J Méd. 2004;350(26):2645-53.
5. Dallegri, F. (1997). Ottonello. Tissue injury in neutrophilic inflammation. Inflamm Res, 46(10):382-91. Comment in: Inflamm Res. 1998;47(6):237-8.
6. e Silva, J. L., Guerreiro, D., Noble, B., Poulter, L. W., & Cole, P. J. (1989). Immunopathology of experimental bronchiectasis. *Am J Respir Cell Mol Biol*, *1*(4), 297-304.
7. Haslett, C. (1999). Granulocyte apoptosis and its role in the resolution and control of lung inflammation. Am J Respir Crit Care Med.;160(5 Pt 2):S5-11.
8. Jeffery, P.K. (1999). Inflammation in chronic obstructive lung disease. Am J Respir Crit Care Med.;160:S3-S4.
9. Liu, C. C., Young, L. H., & Young, J. D. E. (1996). Lymphocyte-mediated cytolysis and disease. *New England Journal of Medicine*, *335*(22), 1651-1659.
10. Majo, J., Ghezzo, H., & Cosio, M. G. (2001). Lymphocyte population and apoptosis in the lungs of smokers and their relation to emphysema. *European Respiratory Journal*, *17*(5), 946-953.
11. O'Shaughnessy, T. C., Ansari, T. W., Barnes, N. C., & Jeffery, P. K. (1997). Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV1. *American journal of respiratory and critical care medicine*, *155*(3), 852-857.
12. Pauwels, R. A., Buist, A. S., Calverley, P. M., Jenkins, C. R., & Hurd, S. S. (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *American journal of respiratory and critical care medicine*, *163*(5), 1256-1276.
13. Saetta, M., Di Stefano, A., Turato, G., Facchini, F. M., Corbino, L., Mapp, C. E., ... & Fabbri, L. M. (1998). CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*, *157*(3), 822-826.
14. Salamone, G., Giordano, M., Trevani, A.S., Gamberale, R., Vermeulen, M., Schettinni, J., et al. (2001). Promotion of neutrophil apoptosis by TNF-alpha. J Immunol, 166(5), 3476-83.
15. Wagner, J.G., & Roth, R.A. (2000). Neutrophil migration mechanisms, with an emphasis on the pulmonary vasculature. Pharmacol Rev, 52(3), 349-74.