

Pathogenesis of pulmonary emphysema – cellular and molecular events

Patogenia do enfisema pulmonar – eventos celulares e moleculares

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ABSTRACT

Pulmonary emphysema is a chronic obstructive disease, resulting from important alterations in the whole distal structure of terminal bronchioles, either by enlargement of air spaces or by destruction of the alveolar wall, leading to loss of respiratory surface, decreased elastic recoil and lung hyperinflation. For many years, the hypothesis of protease-antiprotease unbalance prevailed as the central theme in the pathogenesis of pulmonary emphysema. According to this hypothesis, the release of active proteolytic enzymes, produced mainly by neutrophils and macrophages, degrades the extracellular matrix, affecting the integrity of its components, especially collagen and elastic fibers. However, new concepts involving cellular and molecular events were proposed, including oxidative stress, cell apoptosis, cellular senescence and failed lung tissue repair. The aim of this review paper was to evaluate the cellular and molecular mechanisms seen in the pathogenesis of pulmonary emphysema.

Keywords: Pulmonary emphysema; Alpha 1-antitrypsin; Oxidative stress; Apoptosis; Cell aging

RESUMO

O enfisema pulmonar é uma doença obstrutiva crônica, resultante de importantes alterações de toda a estrutura distal do bronquíolo terminal, seja por dilatação dos espaços aéreos, seja por destruição da parede alveolar, ocasionando a perda da superfície respiratória, diminuição do recolhimento elástico e hiperinsuflação pulmonar. Por muitos anos, a hipótese do desequilíbrio enzimático proteinase-antiproteinase prevaleceu como tema central na patogenia do enfisema. De acordo com essa hipótese, a liberação de enzimas proteolíticas ativas, produzidas principalmente por macrófagos e neutrófilos, degrada a matriz extracelular, afetando a integridade de seus componentes, particularmente as fibras colágeno e elástica. Entretanto, novos conceitos envolvendo eventos celulares e moleculares foram propostos, incluindo o estresse oxidativo, a apoptose celular, a senescência celular e a falha no processo de reparo do tecido pulmonar. O objetivo deste artigo de revisão foi avaliar os mecanismos celulares e moleculares da patogenia do enfisema pulmonar.

Descritores: Enfisema pulmonar; Alfa 1-antitripsina; Estresse oxidativo; Apoptose; Envelhecimento celular

INTRODUCTION

Laennec, in 1834, after examining autopsy slides of the surface of human lungs, described lung emphysema as a lesion resulting from the atrophy of lung tissue due to hyperinflation⁽¹⁾. Emphysema was then redefined as an “abnormal and permanent dilation of the air spaces distal to the terminal bronchiole”⁽²⁾. Such definition was later modified and “alveolar wall destruction without evident fibrosis” was included⁽³⁾.

Currently, pulmonary emphysema may be defined as a chronic obstructive process, resulting from important alterations of the whole distal structure of the terminal bronchiole, called acinus, due to dilation of air spaces or destruction of alveolar wall, causing loss of respiratory surface and blood flow, decrease in elastic recoil and pulmonary hyperexpansion⁽⁴⁻⁵⁾. Such anatomic changes may impact only part of the acinus or the whole acinar structure, indicating the etiology and the pathophysiologic behavior of the disease⁽⁵⁾.

The centriacinar emphysema presents the pulmonary acinus, impaired by enlargement or destruction of the respiratory bronchioli, mostly in apical zones, associated to smoking habits⁽⁶⁾. Panacinar emphysema, found in patients with alpha-1-antitrypsin deficiency⁽⁷⁾ and associated to centriacinar emphysema in patients who smoke, results from a simultaneous and uniform destruction of the alveolar walls and a diffuse enlargement of the pulmonary acinus, mainly in basal zones⁽⁶⁾. Both types of emphysema may be found in patients with chronic obstructive pulmonary disease (COPD), in which, approximately, half of the patients present both forms of pulmonary emphysema, and about 25% present only one form of emphysema⁽⁶⁾.

The distal acinar or paraseptal emphysema affects the peripheral region of the acinus, ducts and alveoli, wrapping them in an air layer, longitudinally to the interlobular septa⁽⁸⁾. The localized paraseptal

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emphysema is associated to spontaneous pneumothorax in young adults and pulmonary bullae in the elderly. Unilateral emphysema or MacLeod syndrome is a consequence of complications from smallpox or adenovirus in childhood, and congenital lobar emphysema usually appears in children before the sixth month of age⁽⁸⁾.

PATHOGENESIS OF PULMONARY EMPHYSEMA

Many processes seem to be involved in the pathogenesis of pulmonary emphysema. However, the hypothesis of the proteinase-antiproteinase enzymatic unbalance has prevailed as central theme in the last few years. According to this hypothesis, the destruction of the alveolar wall results from the action of active proteolytic enzymes that degrade the extracellular matrix (ECM) and affect the integrity of its components, specially the collagen and elastic fibers⁽⁹⁾.

This concept was created based on two observations:

- a) subjects with alpha-1-antiprotease deficiency, considered a genetic defect transmitted by an autosomal recessive gene, usually develop severe pulmonary emphysema early in life⁽⁸⁾;
- b) experimental models of pulmonary emphysema are based on nebulization or instillation of proteolytic enzymes, such as papain (*Carica papaya*)⁽⁵⁾, porcine pancreatic elastase⁽¹⁰⁾ and human neutrophilic elastase⁽¹¹⁾. That proteolytic process, associated to the uniform destruction of the ECM of the pulmonary acinus, results in morphophysiological and histological changes in the lungs, equivalent to those seen in emphysema in human beings⁽⁹⁾.

The hypothesis of the pulmonary emphysema is related to alpha-1-antiprotease deficiency – which has inhibitory activity over the neutrophil elastase more promptly than over other proteinases⁽¹²⁾ – or to the increased elastolytic activity – resulting from the accumulation and activation of neutrophils in smokers, when compared to non-smokers⁽⁹⁾ – suggests the action of neutrophil proteinases as decisive to the development of emphysema. In an analysis of the inflammatory cells – present in the pulmonary parenchyma and in the terminal air spaces in lungs surgically removed from patients with mild or severe emphysema and patients without emphysema – an increased number of neutrophils, macrophages, T-lymphocytes and eosinophils was seen in the emphysematous tissue⁽¹³⁾. These cells have a 10-fold increase in the lungs with severe emphysema, when compared to normal lungs⁽⁹⁾. In advanced stages of COPD (associated to severe airway obstruction, especially in peripheral airways,

and to a fast reduction in lung function), there is an increase in the neutrophil infiltrate⁽¹⁴⁾. Stringer et al. demonstrated that the phagocytic action of neutrophils is impaired when they are exposed to cigarette smoke extract⁽¹⁵⁾. Not only the neutrophils, but also the alveolar macrophages present dysfunctions when exposed to cigarette components. Alveolar macrophages are predominant cells in the airways and play an essential role in the genesis of emphysema, by means of releasing leukotrienes, prostaglandins, cytokines, chemokines, metalloproteinases (MMP) and reactive oxygen species⁽¹⁶⁾. Analyzing the bronchial submucosa of patients with COPD, one sees that the predominance of alveolar macrophages correlates to severity of the disease⁽¹⁷⁾. Macrophages of smoking patients express an increase in the antiapoptotic protein B-cell leukemia/lymphoma (Bcl-X_L), suggesting that cigarette-smoke-induced oxidative stress may contribute to chronicity of the airway inflammation, associated to decreased cell apoptosis⁽¹⁸⁾. Kirkham et al. observed, in *in vitro* studies, that in human macrophages exposed to cigarette smoke, the ability of such cells to phagocytose apoptotic neutrophils was reduced⁽¹⁹⁾. Moreover, the release of neutrophilic, macrophilic and proteolytic enzymes induce the degradation of the ECM elastic component, as observed in experimental models⁽²⁰⁾, as well as in human emphysematous patients⁽²¹⁾. Besides the elastic component of the ECM, these proteolytic enzymes showed remodeling and increased synthesis of collagen^(10,22).

Under normal conditions, there is a balance between the production of aggressive and protecting substances in the pulmonary acinus. However, prolonged smoking habits, associated to oxidative stress, induce the unbalance of such substances. The reactive oxygen species (ROS), derived from the cigarette-smoke oxidative stress, promote the activation of the kappa B (NF-κB) nuclear factor and activator protein 1 (AP1), which may enhance inflammatory response in COPD lungs. Moreover, MAP kinases (MAPK) and phosphatidylinositol 3-kinase (PI3K) are also activated by ROS⁽²³⁻²⁴⁾. Experiments with small rodents exposed to ozone confirmed NF-κB and p38 MAPK activation in lung cells⁽²⁵⁾. Di Stefano et al. demonstrated a higher expression of the nuclear factor NF-κB in bronchial cells of COPD patients⁽²⁶⁾. A similar result was observed in lungs of patients with COPD, in which the increase in the expression of nuclear factor NF-κB is associated to the degradation of the NF-κB (I-κB)α inhibitor⁽²⁷⁾. Oxidative stress may also cause I-κBα phosphorylation and its subsequent degradation into some typical cells⁽²⁸⁾.

Also to be considered in the pathogenesis of pulmonary emphysema is the rate between cell

senescence and oxidative stress. Junqueira et al. demonstrated that oxidative stress may gradually develop with aging – as a consequence of an increase in plasma levels of products derived from lipid peroxidation and of the activation of antioxidant enzymes present in the erythrocytes circulating in the blood system – as the nutritional antioxidants plasmatic levels decrease⁽²⁹⁾. The lungs are continuously exposed to endogenous oxidants, mainly generated from phagocytic cells, or exogenous factors derived from atmospheric pollutants and mainly cigarette smoke⁽³⁰⁾. Patients with chronic obstructive pulmonary disease expressed an increase in oxidative stress biomarkers in the lungs⁽³¹⁾, as well as in the respiratory muscles⁽³²⁾. Studies conducted in SMP30 knockout rats showed increased airspace without alveolar destruction, revealing a new model of senile lung⁽³³⁻³⁴⁾.

Nevertheless, SMP30 knockout rats exposed to cigarette smoke demonstrated, besides an increase in aerial space, destruction of the alveolar wall, associated to increase in oxidative stress⁽³⁵⁾. Nyunoya et al. experimentally demonstrated that one single exposition to cigarette smoke can inhibit fibroblast proliferation (cells that are essential to promote lung repair after damage). Multiples expositions to cigarette smoke take these cells to an irreversible state of senescence⁽³⁶⁾. These cells, in turn, are not able to repair the pulmonary parenchyma and thus contribute to the development of emphysema⁽³⁷⁾. In addition, senescent cells cannot synthesize proteins⁽³⁶⁾. Such evidences indicate a possible involvement of cell senescence in the pathogenesis of pulmonary emphysema.

However, the fact that only a minority of smokers develop the disease suggests the existence of other risk factors, besides those mentioned above, in the genesis of pulmonary emphysema. Studies in relatives of patients with pulmonary emphysema clearly demonstrated the importance of the genetic factor in determining individual susceptibility to the disease⁽³⁸⁾. Experimental studies in mice exposed to cigarette smoke⁽³⁹⁾, or after genetic modification⁽⁴⁰⁾ indicate the appearance of morphophysiological changes compatible with pulmonary emphysema.

Even though the hypothesis of proteinase-antiproteinase enzyme unbalance prevails in the pathogenesis of pulmonary emphysema, it is not clear yet whether the development of the disease is due to excessive proteases or alpha-1-antiprotease deficiency, or both. Nevertheless, the cellular and molecular and autoimmune phenomena, alveolar cell apoptosis and genetic factors must also be considered, since – together or isolate – they contribute to understanding of the pathophysiology of pulmonary emphysema.

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