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Pathogenic Mechanisms in Emphysema: From Protease Anti-Protease Imbalance to Apoptosis

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1. Introduction

In 1963, Laurel and Erickson reported their discovery of severe α_1 -antitrypsin (AAT) deficiency and its association with emphysema (Laurell & Erickson, 1963). Soon after, Gross and coworkers reported that emphysema was induced in rats by the intratracheal instillation of a proteolytic enzyme (Gross et al., 1965). These findings led to the proteolytic hypothesis of emphysema (Janoff, 1985) which considers that emphysema develops as a result of the smoking-induced release of proteolytic enzymes from the increased number of neutrophils and macrophages in the lung. Proteolysis of lung connective tissue (more specifically elastin) occurs because the released proteases may not be fully inhibited by antiproteases, resulting in emphysema. However, although proteolysis may have a significant pathogenic role particularly in AAT deficiency, other pathogenic mechanisms, such as oxidants either from inhaled smoke or from inflammatory cells, inflammation, T lymphocyte cell mediated immunity, and apoptosis have a significant pathogenic role (MacNee, 2005).

This chapter, based on a previous review article (Abboud & Vimalanathan, 2008), updated and revised following a Pub-Med search, and will cover protease-antiprotease imbalance and apoptosis, as pathogenic mechanisms in emphysema. The pathogenic role of oxidants, inflammatory cells, and cell mediated immunity will be covered in other chapters.

2. Protease-antiprotease imbalance in severe antitrypsin deficiency

The hypothesis that the main pathogenic mechanism in emphysema in severe AAT deficiency is due to protease-antiprotease imbalance, is well supported by evidence since AAT is the main inhibitor of neutrophil elastase. Since this topic will be discussed in detail in another chapter, this paragraph will serve as a brief introduction. In severe AAT deficiency, anti-elastase protection in the lung interstitium and alveolar space is markedly decreased in proportion to the decreased plasma levels to about 15-20 % of normal, and does not fully protect the lung against released neutrophil elastase. Neutrophil elastase is a potent elastolytic enzyme, which induces emphysema when injected intratracheally in

experimental animals (Janoff et al.,1977; Senior et al,1977). Smoking increases the number of neutrophils in the lung, and induces the release of neutrophil elastase (Fera et al., 1986; Abboud et al. 1986). The released neutrophil elastase may not be fully inhibited by the severely deficient AAT levels leading to proteolytic activity and the development of emphysema. The positive correlation between increased leucocyte elastase concentration and severity of emphysema in patients with severe AAT deficiency, supports a pathogenic role for neutrophil elastase in AAT deficient emphysema (Kidokoro et al.,1977).

3. Protease antiprotease imbalance in copd without severe antitrypsin deficiency

In contrast, in smokers with COPD without AAT deficiency , there is less evidence to support protease antiprotease imbalance as a pathogenic mechanism in emphysema, compared with AAT deficient smokers, because there is no definitive evidence of severe antiprotease deficiency to lead to unopposed proteolysis in the lung. Smoking may cause a protease-antiprotease imbalance in the lung by decreasing the functional activity of AAT and other protease inhibitors in the lung interstitium and "alveolar" lining fluid, and by increasing the amount of elastolytic proteases released in the lung. Some studies reported that smokers had decreased anti-elastase activity of AAT in BAL, compared with nonsmokers (Gadek et al., 1979; Carp et al., 1982). However, this reported degree of inactivation was not confirmed by later studies (Stone et al.,1983; Boudier et al., 1983; Abboud et al., 1985).

3.1 Studies evaluating neutrophil elastase in emphysema

Cigarette smoking can induce the release of neutrophil elastase (NE) in BAL of healthy volunteers (Fera et al.,1986), and intense smoking can acutely increase plasma NE levels (Abboud et al., 1986). NE released in the lung may be taken up and internalized by alveolar macrophages (AM) (Campbell et al., 1979) . A study evaluating BAL in 28 patients with COPD supported a role for NE and protease-antiprotease imbalance by showing that NE levels in BAL correlated directly and BAL anti-elastase activity correlated inversely with emphysema, assessed by CT scan and carbon monoxide diffusing capacity (Fujita et al.,1990). Another study of older volunteers reported increased levels of NE in AM of smokers with CT scan evidence of emphysema (Betsuyaku et al.,1995), suggesting that NE release in the lung and its uptake by AM could have been a pathogenic factor in emphysema. NE bound to elastin may continue to degrade elastin despite the presence of active AAT in the surrounding medium (Morrison et al., 1990). All these findings support a potential role for NE in the development of human emphysema, despite the lack of severe inactivation of AAT in the lung. The pathogenic role of NE was also confirmed in a mouse NE-knockout exposed to cigarette smoke, where the resulting emphysema was reduced by 59% compared with control smoke-exposed mice (Shapiro et al., 2003). This was not all a direct effect of the absence of NE activity, but partly secondary to decreased macrophage recruitment in the absence of NE; it could be also partly due to the lack of degradation by NE of tissue inhibitors of metalloproteases which inhibit macrophage elastase activity.

3.2 Potential role of macrophage proteases in emphysema

It is likely that macrophage proteases have a pathogenic role for in human emphysema. Investigators reported that young smokers dying accidentally had an increased number of macrophages in the respiratory bronchioles (Niewoehner et al., 1974), in the same region where centrilobular emphysema develops in smokers without AAT deficiency. Morphometry of resected human lungs indicated that the extent of emphysema was directly related to the numbers of AM but not neutrophils (Finkelstein et al., 1995). These two studies suggested a potential role of macrophages in emphysema. Elastolysis by AM *in vitro* was not inhibited by AAT, while that of neutrophils was inhibited (Chapman et al., 1984; Chapman & Stone 1984). This finding supported a pathogenic role for AM elastolytic enzymes in emphysema, since these AM enzymes would not be inhibited by AAT, the major protease inhibitor in plasma and interstitial fluid. Subsequently, investigators demonstrated several elastolytic enzymes in human AM: cathepsins L and S (Reilly et al., 1989; Reilly et al., 1991; Shi et al., 1992), the matrix metalloproteases (MMPs) MMP-2 and MMP-9, previously termed 72 & 92 kDa collagenases respectively (Senior et al., 1991) and MMP-12 also named macrophage metallo-elastase (Shapiro et al., 1993). In addition, interstitial collagenase or MMP1, a non-elastolytic enzyme, induced emphysema in transgenic mice expressing MMP1 (D'Armiento et al., 1992; Foronjy et al 2003), by degrading type III collagen (Shiomy et al., 2003).

Several studies support a pathogenic role for AM in human emphysema, by comparing findings in subjects with and without emphysema. Cultured AM from patients with emphysema showed increased elastolytic activity compared with that of AM from patients with bronchitis or other lung diseases (Muley et al., 1994). In a study of 34 healthy smokers (mean age 46 yr), there was a significantly greater AM cell counts in BAL in those with emphysema by computed tomography (CT) compared to those without emphysema; this finding indicated a greater AM elastase load in the lungs in those with emphysema, since the AM elastolytic activity/cell was similar in the two groups (Abboud et al., 1998). AM obtained by BAL from 10 emphysema patients, had increased expression of MMP9 and MMP1, when compared with 10 matched controls (Finlay et al., 1997). Emphysematous lung tissue had significantly higher levels of MMP9 and MMP2 compared with control non-involved lung tissue; and showed elastolytic activity corresponding to MMP2 and MMP9 (Ohnishi et al., 1998). A study using immunohistochemistry of lung tissue, showed increases in MMP1, MMP2, MMP8, and MMP9 in lung tissue from COPD patients compared with controls (Segura-Valdez et al., 2000). There was increased expression of MMP1 in the lungs of patients with emphysema (Imai et al., 2001); however, the MMP1 was localized to the type II epithelial cells and not macrophages.

Cigarette smoke induced emphysema in mice requires MMP12; mice homozygous for a knockout of the MMP12 gene, in contrast to controls, did not develop emphysema in response to cigarette smoke exposure (Hautamaki et al., 1997). However, MMP12 is much more highly expressed in mice compared with humans. A study in COPD patients reported that the number of AM in BAL expressing MMP12 and the level of MMP12 expression was higher in COPD than in controls (Molet et al., 2005). Increased MMP levels by ELISA in induced sputum from 26 stable COPD patients were significantly higher than healthy smokers, never smokers, and former smokers (Demedst et al., 2006); in addition MMP12 enzyme activity in the COPD subjects was markedly increased compared with non-smokers. These two studies support a potential pathogenic role for MMP12 in human emphysema.

Smoking and pro-inflammatory stimuli can induce message expression of AM elastases and proteases, which could lead to protease-antiprotease imbalance. Smokers have increased expression of cathepsin L in AM compared to non-smokers (Takahashi et al., 1993), and also increased activity of cathepsin S in AM lysates (Reilly et al., 1991). Pro-inflammatory mediators induce expression of MMPs, such as the marked increase in mRNA for MMP12 in cultured AM by lipopolysaccharide (LPS) (Shapiro et al., 1993). TNF- α and IL-1 β increased expression of MMP9 by human macrophages without increasing its inhibitor, tissue inhibitor of metalloprotease (TIMP1) (Saren et al., 1996); these two cytokines, which are increased in COPD, may thus lead to a protease-antiprotease imbalance between MMP9 and its inhibitor. The release of TNF- α in mice by cigarette smoke was dependent on MMP-12 (Churg et al., 2003), and was abolished in MMP12 knockout mice; TNF- α accounted for 70% of the smoke induced emphysema in the mouse (Churg et al., 2004). In-vitro studies showed that AM from patients with COPD released more MMP9 than AM from healthy smokers, and MMP9 release was increased by IL-1 β , LPS, and cigarette smoke solution (Russell et al., 2002a). The same investigator reported that MMPs, cysteine and serine proteases contributed to the in-vitro elastolysis by human AM during the 72 hr evaluation (Russell et al., 2002b), indicating the difficulty in implicating a specific protease in lung destruction.

A recent study (Omachi et al., 2011) evaluated plasma MMP9 levels in relation to progression of emphysema over a period of one year, in 126 subjects with severe AAT deficiency who were on placebo treatment in a clinical trial evaluating AAT augmentation therapy. They found that higher baseline plasma MMP-9 levels were associated with lower values of FEV₁ and CO diffusing capacity ($p=0.03$), but not CT scan lung density. Moreover, MMP-9 levels predicted a decline in CO pulmonary diffusing capacity ($p=0.04$) and worsening lung density by CT scan ($p=0.003$). This relationship may not apply in human emphysema without severe AAT deficiency. A thorough and elaborate study evaluated the role of MMP9 in cigarette smoke induced emphysema in mice and humans (Atkinson et al., 2011); I will restrict my review to the human findings. Macrophage MMP-9 mRNA isolated by laser capture micro-dissection from 5 human lungs obtained at the time of lung transplantation were similar in areas of lung with and without emphysema. The investigators also enrolled subjects who had completed a National Lung Screening Trial and were free of cancer or an inflammatory or immune disorder into their emphysema biomarker study. Of these 38 had a CT scan emphysema index $>10\%$ and were considered to be "emphysema-sensitive", while 47 had an emphysema index of $<5\%$ and were "emphysema-resistant" controls. Circulating monocyte MMP9 mRNA showed a positive correlation with emphysema index for all subjects ($p=0.02$), and a more significant correlation in the "emphysema-sensitive" group ($p=0.01$), but there was no statistical difference in results between the two groups. There was no correlation of circulating monocyte MMP9 mRNA with the lung injury markers used, Clara cell secretory protein and surfactant protein-D. It would be interesting to check the correlation of emphysema extent with MMP9 plasma levels, which may be a better marker of MMP9 release in the lungs than levels in circulating monocytes.

In studies from my laboratory on alveolar macrophages (AM) lavaged from resected lung specimens, the level of mRNA expression of MMP1 in AM showed a significant positive correlation with the extent of emphysema by CT scan (Wallace et al., 2008). In addition, MMP12 mRNA expression was increased in current smokers vs ex-smokers, and there was

there was a significant negative correlation between MMP12 gene expression and carbon monoxide diffusing capacity. These results support a pathogenic role for both MMP1 and MMP12 in human emphysema. A pathogenic role for cathepsin K in the development of emphysema was demonstrated in smoke-exposed guinea pigs compared with controls, and there were also data supporting increased expression of cathepsin K in lungs of emphysema patients (Golovatch et al., 2009).

Fig 1 is a diagram of potential mechanisms leading to protease antiprotease imbalance and emphysema.

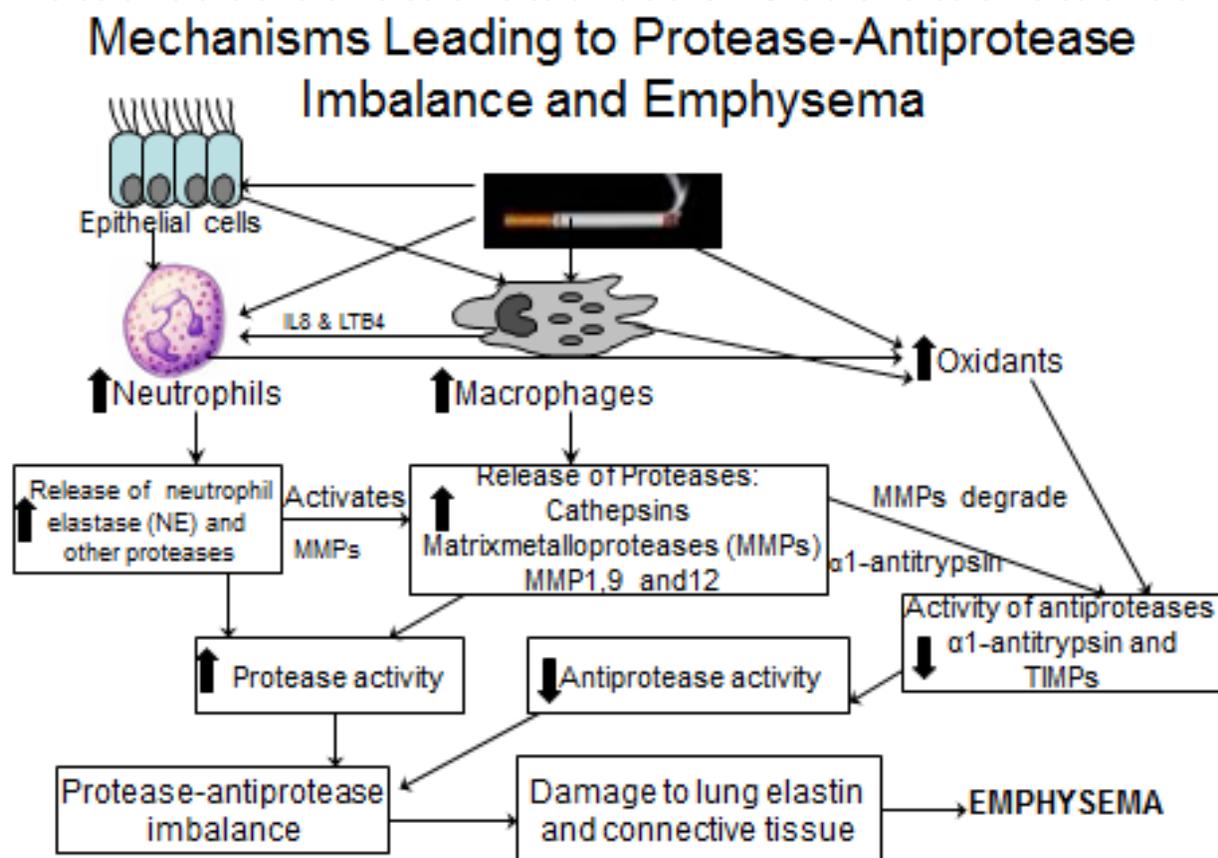


Fig. 1. Diagram showing the pathways leading to smoking-induced protease-antiprotease imbalance in the lung. (Reproduced from Abboud, R. , & Vimalanathan, S. (2008), with permission of the publisher, Int J Tuberc Lung Dis)

Smoking induces epithelial cells to produce cytokines which stimulate neutrophils and macrophages. Cigarette smoke also acts directly on neutrophils and macrophages to activate them . Cigarette smoke has oxidants which can inactivate antiproteases, in addition to antiprotease inactivation by oxidants released by macrophages and neutrophils.

The stimulated neutrophils and macrophages release proteolytic enzymes. Neutrophil elastase can activate MMPs, while MMPs can inactivate α_1 -antitrypsin. Not shown in the diagram, is the role of MMP-12 in releasing TNF- α , which amplifies the inflammatory reaction. These processes lead to a protease-antiprotease imbalance, which can degrade lung elastin and connective tissue; if sustained, this will lead to emphysema.

3.3 Role of polymorphisms in MMPs

An MMP polymorphism (C-15621) was associated with emphysema by CT scan in one Japanese study (Minematsu et al., 2001) and with upper lobe emphysema in another Japanese study (Ito et al., 2005), and with COPD in a Chinese population (Zhou et al., 2004).

A study from Russia evaluated gene polymorphisms of G(-1607)GG of MMP1, C(-1562)T of MMP9, and A(-82)G of MMP12, and found the frequencies did not differ significantly between 318 COPD patients compared with 319 healthy controls (Korytina et al., 2008). However, the (-1562)T allele of MMP9 was significantly higher in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV COPD than in stages II and III, indicating that this allele predisposed to severe disease; it also predisposed to early onset of COPD (age < 55 yr).

A multicentre European study determined 26 single nucleotide polymorphisms (SNP)s, covering reported SNP variations, in MMPs- 1, 9 and 12 from 977 COPD patients and 876 non-diseased smokers of European descent and evaluated their association with disease singly and in haplotype combinations (Haq., et al. 2010). They used logistic regression to adjust for age, gender, centre, and smoking history. They reported that the common A-A haplotypes of two SNPs in MMP-12 (rs652438 and rs2276109), were associated with severe or very severe disease (GOLD Stages III and IV) (p= 0.0039).

This review has focused on neutrophil and macrophages proteases, but proteases from other cells such as lung fibroblasts, and myofibroblasts, and dendritic cells may also be involved.

3.4 Role of the macrophage protease inhibitors TIMPs and cystatin C, and other protease inhibitors in emphysema

It is likely that it is the balance between macrophage proteases and their respective antiproteases that has a pathogenic role in emphysema. TIMPs are the endogenous inhibitors of MMPs; human AM release TIMP1 and TIMP2 (Shapiro et.,1992). AM from COPD patients release less TIMP1 *in vitro* than those from smokers without COPD and non-smokers (Pons et al., 2005), predisposing to proteolysis by MMPs. TIMP3 is the only TIMP that binds strongly to the extracellular matrix. TIMP3 knockout mice demonstrate progressive airspace enlargement and enhanced collagen degradation without inflammation or increased elastin breakdown (Leco et al., 2001). However, there are no reported associations between TIMP 3 polymorphisms and COPD. A polymorphism in the TIMP2 gene (G853A) was associated with COPD in a Japanese study (Hirano et al., 2001), and in an Egyptian population (Hegab et al., 2005).

Cystatin C is present in most biological fluids, and is a potent inhibitor of cathepsins. Cystatin C is a major product of AM (Chapman et al., 1990) and is secreted by AM from smokers at higher levels than non-smokers (Warfel et al., 1991) The concentrations of cathepsin L and its inhibitor cystatin C were both significantly increased in BAL fluid from smokers with emphysema compared with those without emphysema; however there was no significant difference in cathepsin L activity in BAL between the two groups (Takeyabu et al., 1998). There are no reports of deficiency or polymorphisms in cystatin C in relation to emphysema or COPD.

Polymorphisms in the Serpina2 gene, which encodes the protease nexin1 (plasminogen activator inhibitor type 1), were associated with COPD in a Boston population study (Demeo

et al., 2006), and validated in two large family-based and case-control association studies (Zhu et al., 2007). Polymorphism of the SERPINA2 gene was also recently found associated with emphysema in consecutive autopsy cases in Japan (Fujimoto et al., 2010). Decreased activity of the plasminogen activator inhibitor type 1 in the lung can lead to increased activity of plasminogen, which can promote lung matrix degradation (Chapman et al., 1984).

3.5 Role of oxidants in protease-antiprotease imbalance

As indicated in a previously quoted review article on pathogenesis of COPD (MacNee, 2005), oxidants have a significant pathogenic role in COPD. The gaseous phase of cigarette smoke contains many reactive oxidants such as superoxide anion, nitric oxides and peroxy nitrates, as reviewed recently (MacNee 2005; Lin & Thomas 2010). Oxidants and free radicals inhaled in tobacco smoke, can damage airway epithelial cells, and impair antioxidants, such as glutathione to non-reducible glutathione-aldehyde derivatives (van Der Toorn et al., 2007). Oxidants from tobacco smoke may also inactivate antiproteases, predisposing to a protease-antiprotease imbalance from the increased numbers of neutrophils and macrophages in smokers' lungs. Oxidants from cigarette smoke may also directly damage components of the lung connective tissue matrix, and interfere with elastin repair and synthesis (MacNee & Tudor 2009). Neutrophils and macrophages themselves when activated also release oxidants, such as superoxides, and nitric oxides, and contribute to the oxidative burden. Although antioxidants such as glutathione, catalase and superoxide dismutase protect the tissues against oxidants, the oxidant/antioxidant balance may tip in favor of oxidants leading to oxidative stress.

Patients with COPD have increased levels of hydrogen peroxide and of 8-isoprostane (a peroxidation product of arachidonic acid) in exhaled breath condensates compared with controls (MacNee 2005). Healthy smokers had reduced histone deacetylase activity in bronchial biopsies and in alveolar macrophages obtained by lavage, when compared with age matched nonsmoking controls (Ito, K., et al., 2001). These investigators also demonstrated that smoking resulted in a greater release of TNF- α from the alveolar macrophages when stimulated by IL-1 β , which they considered was due to the suppressive effect of smoking on histone deacetylation. This suppressive effect on histone deacetylation results in increased acetylation, causes local unwinding of DNA, and allows increased inflammatory gene expression, which may contribute to the development of COPD. A later study confirmed decreased histone deacetylase activity in resected lungs of COPD patients, and concluded that there was a progressive decrease in activity with increasing severity of COPD (Ito, K., et al., 2005). They also reported increased expression of IL-8 mRNA in lung tissue in COPD.

Oxidative stress may be determined non-invasively by measurement of oxidation products in exhaled breath condensates. According to a recent review article, the following markers of oxidative stress have been increased in exhaled breath condensates of subjects with COPD: hydrogen peroxide, nitrite, nitrosothiols, 8-isoprostane, and thiobarbituric acid reactive substances (Lee & Thomas, 2009). Oxidative stress is also indicated by the presence of biomarkers in blood indicative of lipid peroxidation, such as 4-hydroxy-2-nonenal (MacNee & Tudor 2009; Fischer, B.M., et al., 2011). The latter recent review article (Fischer, B.M., et al., 2011) also quoted published reports of increased levels of 4-hydroxy-2-nonenal, in both airways and alveoli of COPD patients, and also increased blood levels of

malondialdehyde (an end product of lipid peroxidation) in COPD due to tobacco smoking as well as wood smoke exposure. 4-hydroxy-2-nonenal can increase gene expression of pro-inflammatory mediators such as IL-8, monocyte chemoattractant protein-1 (MacNee & Tudor 2009). Reactive oxygen species can also directly or indirectly induce pro-inflammatory mediators such as IL-1, TNF- α , IL-6, and IL-8 (Rahman & Adcock 2006).

The mRNA of inflammatory cytokines, chemokines, oxidant and antioxidant enzymes, proteases and antiproteases was evaluated in peripheral lung tissues from 14 COPD subjects and compared with 19 subjects without COPD undergoing lung resection for lung cancer (Tomaki, M., et al., 2007). They reported that mRNA, for catalase, two glutathion S-transferases, microsomal epoxide hydrolase, and TIMP2 were significantly decreased in COPD lung tissues compared with the non-COPD controls. On the other hand, the expressions of mRNA for IL-1 β , IL-8, and monocyte chemoattractant protein-1 (MCP-1) were significantly increased in COPD lungs. Most of these changes were also associated with cigarette smoking. Their data suggest that in addition to the impairment in antioxidant defenses, upregulation of cytokines and chemokines may be involved the development of COPD.

3.6 Role of inflammatory mediators and cytokines in protease-antiprotease imbalance

The last paragraph of page 4, reviewed the effects of TNF- α and IL-1 β , on inducing expression of MMP9 by human macrophages without increasing its inhibitor TIMP1, predisposing to possible protease-antiprotease imbalance. In this section, I will briefly discuss these 2 pro-inflammatory cytokines and an additional one IL-8, which have been included in a review article on inflammatory mediators (Chung, K.F., 2005).

Imbalances between IL-1 β and its antagonists in COPD have been reported in 15 patients with stable COPD compared with age matched healthy controls (Sapey, E., et al., 2009). Although mean concentrations of IL-1 β in COPD were not different from controls, mean concentrations of their receptor antagonists (IL-1RA & IL-1sRII) were markedly reduced, suggesting that IL-1 β may have pathogenic role in COPD. In contrast, there were no difference in TNF- α and its antagonists in COPD patients compared with controls. A case control trial in Egyptian subjects over 60 years compared 3 groups of 30 subjects matched by age and sex, consisting of healthy subjects, COPD without any comorbidities, and COPD with cardiovascular disease but no other comorbidities (Amer, M.S., et al., 2010). There was no significant difference in the serum levels of IL-1 β , TNF- α , or C reactive protein (CRP) between the control subjects and the COPD subjects with no cardiac disease. The group with cardiovascular disease had increased IL-1 β and CRP (but not TNF- α) levels compared with the other 2 groups. However, the increase in IL-1 β and CRP cannot be definitely attributed to the more severe COPD in the 3rd group, since it could be secondary to the cardiovascular comorbidity.

A study from Korea evaluated four potentially functional polymorphisms in the IL-1 β in 311 COPD patients and 386 healthy controls and found polymorphisms that significantly increased the odds ratio of developing COPD (Lee, J.M., et al., 2008). In addition, they reported that a polymorphism in the IL-1 β receptor antagonist gene IL-1RN afforded some protection.

Induced sputum from patients with moderate to severe COPD, had increased neutrophils, and increased levels of IL-8 and TNF- α , when compared with that of healthy cigarette

smokers and normal non-smoking controls, (Keatings, V.M., et al., 1996). The increase in IL-8 was confirmed in a later study evaluating IL-8 in bronchoalveolar lavage fluid of COPD patients compared with controls (Pesci, A., et al., 1998).

Cytokine mRNA for IL-8, macrophage inflammatory protein-1 α (MIP-1 α), and MCP-1 were quantified using laser-capture microdissection of human bronchial epithelial cells and alveolar macrophages (Fuke, S., et al., 2004). The authors found that mRNA levels for IL-8, MIP-1 α and MCP-1 were higher in bronchial epithelial cells of smokers with airflow obstruction and/or emphysema, compared with results in smokers without airflow obstruction or emphysema. However, there was no difference in macrophage mRNA levels for these cytokines between the 2 groups. Their findings support the role of the bronchiolar cells as the source of these increased chemokine levels in early COPD.

Although TNF- α has a major pathogenic role in experimental emphysema (Churg, A., et al., 2004), it does not appear to be as implicated in emphysema in human COPD. One study compared gene polymorphism in 169 Dutch COPD patients compared with Dutch controls, and reported an increased frequency of the G/A genotype in patients without radiological emphysema (Kucukaycan, M., et al., 2002). Another study from Italy compared 63 male patients with COPD with 86 healthy controls, and found no difference in gene polymorphisms between the two groups (Ferrarotti, I., et al., 2003).

It is likely that the pathogenic role of mediators and cytokines will be elucidated in multicenter studies evaluating pathogenetic mechanisms in COPD in association with large longitudinal clinical trials.

3.7 Role of T-lymphocytes and cell mediated immunity

Smokers with symptoms of chronic bronchitis and airflow limitation undergoing lung resection for a localized lesion were found to have increased numbers of CD8+ T-lymphocytes infiltrating the airway wall, which were increased compared with smokers with normal lung function, while the number of neutrophils, macrophages, and CD4+ T-lymphocytes were similar in the two groups (Saetta, M., et al., 1998). This suggested a pathogenic role for CD8+ lymphocytes in the development and progression of COPD. The subject of the role of lymphocytes in COPD is well covered by a recent review article (Gadgil & Duncan 2008). T lymphocytes can cause tissue injury either directly by cytolysis or by secreting pro-inflammatory mediators. Moreover, peripheral T-cells, specially CD8+ cells are activated and secrete mediators (Gadgil, A., et al., 2006). CD8+ lymphocytes appear to have a role in the development and progression of COPD, as quoted from several references in the review (Gadgil & Duncan 2008). CD8+ T-lymphocytes can mediate cell death directly through secretion of cytotoxins such as granzyme and perforins, as quoted from other references (Gadgil & Duncan 2008).

CD4+ T-cells can initiate downstream immune processes by releasing activating cytokines, can amplify inflammatory reactions by other immune cells, and are essential for full adaptive immune cytotoxicity by lowering the threshold of activation and promoting survival of CD8+ T-cells (Gadgil & Duncan 2008). In addition, CD4+ T-cells are important for the activation of antibody producing B-cells. In a previous study, they reported finding circulating IgG autoantibodies against epithelial cells in about 70% of their COPD patients, as compared with 10% of non-smoking controls, and 13% of cigarette smokers without

evidence of lung disease (Feghali-Bostwick, C.A., et al., 2008). There was also immune complex deposition in six end stage explanted lungs. These autoantibodies may have a pathogenic role in airway epithelial injury in COPD. Also, a number of studies indicate that the lymphocyte proliferations in COPD are driven by peptide antigens, and consider various possibilities such as microbial peptide antigens, adenoviral antigens, tobacco smoke related peptides, elastin peptides, and auto-antigens from apoptotic cells and cellular debris (Gadgil & Duncan 2008).

4. Apoptosis and emphysema

This is an exciting new area of intense investigation which will further elucidate pathogenetic mechanisms in emphysema and is likely to lead to specific therapies in the future. Apoptosis refers to programmed cell death, affecting the endothelial capillaries and the alveolar epithelium leading to the development of emphysema. This area of investigation was initiated by the landmark study reporting that chronic blockade of Vascular Endothelial Growth Factor (VEGFR) receptors in rats by a chemical SU5416, induced alveolar septal apoptosis and enlargement of the air spaces indicating emphysema (Kasahara et al., 2000). The apoptosis was mediated by caspase 3, a proteolytic enzyme inducing apoptosis, and was prevented by treatment with a caspase inhibitor. The topic of apoptosis is covered by recent reviews (Demedts et al., 2006; Tudor et al., 2006, Morissette et al., 2009, Macnee & Tudor 2009). Additionally, specific sections about alveolar cell apoptosis and proliferation, aging and senescence, as well as mediators and signaling pathways, are also covered in a comprehensive review article about the pathobiology of cigarette smoke-induced COPD (Yoshida & Tudor, 2008). The pathways in apoptosis are involved, but may be simplified to an extrinsic and intrinsic pathway, The extrinsic pathway is activated by extracellular death ligands, such as those related to TNF- α which result in activation of caspases (proteolytic enzymes involved in apoptosis). The intrinsic pathway is triggered by cellular or DNA injury leading to the release of cytochrome C and apoptosis.

4.1 Human studies

Investigators studying human lung specimens to evaluate MMPs by immunohistochemistry in lungs with emphysema compared with controls, also evaluated apoptosis by terminal deoxynucleotide transferase-mediated dUTP nick-end labeling (TUNEL) assays, and were the first to report increased endothelial cell apoptosis and, to a lesser extent alveolar epithelial apoptosis in emphysema (Segura-Valdez et al., 2000). In 2001, the investigators who showed that VEGFR blockade in rats induced apoptosis, reported results from human lungs (Kasahara et al., 2001). The number of apoptotic epithelial and endothelial cells in alveolar septa of emphysema lungs per unit of lung tissue nucleic acid was about double in emphysema compared with normal lungs. In addition, VEGF, its receptor protein and mRNA expression were reduced in emphysema lungs, suggesting that apoptosis due to a decrease in endothelial maintenance factors may have a pathogenic role in emphysema, However another study reported no significant difference in apoptotic index in the lungs of 10 smokers with emphysema compared with 5 smokers without emphysema (Majo et al. 2001). Another group reported increased apoptosis of alveolar epithelial and endothelial cells as well as mesenchymal cells in lung tissue from 10 emphysema patients, compared with 6 controls without emphysema (Imai et al.,2005), and there was significant inverse

correlation of apoptosis with lung surface area. They also evaluated cell proliferation by immunostaining for proliferating cell nuclear antigen (PCNA), and reported that it was increased but was not correlated with apoptosis index or lung surface area. Other investigators evaluated apoptosis by flow cytometry in cells obtained by bronchoalveolar lavage in subjects with COPD, and compared results in 16 exsmokers with 13 current smokers, and 20 non-smoking volunteers (Hodge et al., 2005). There was a mean 87% increase in apoptotic airway epithelial cells in COPD subjects, and a mean doubling of apoptosis by airway T lymphocytes compared with non-smoking volunteers, but there was no difference between COPD subjects still smoking and those who had quit. They concluded that this increased airway cell apoptosis in COPD persists despite smoking cessation.

A study from Japan sought to evaluate the turnover of alveolar wall cells in emphysema by comparing lung tissue specimens from 13 patients with emphysema who had lung volume reduction surgery, 7 asymptomatic smokers and 9 non-smokers undergoing lung resection for solitary lung cancers (Yokohori et al., 2004). They reported that the percentages of alveolar wall cells undergoing apoptosis and proliferation were higher in the emphysema patients than asymptomatic smokers or non-smokers. They concluded that emphysema is a dynamic process in which both alveolar cell wall apoptosis and proliferation are recurring. The same investigators also demonstrated that activated caspase 3 (an enzyme inducing apoptosis) when instilled into the lungs of mice resulted in alveolar wall destruction and emphysema (Aoshiba et al., 2003). A study of 16 end-stage lungs from subjects undergoing lung transplantation for advanced emphysema (7 were due to AAT deficiency) were compared with 6 unused donor lungs (Calabrese et al., 2005). The apoptotic index was significantly increased in the emphysema lungs compared with controls, but the alveolar proliferation was similar in emphysema and control lungs. They concluded that there was a marked imbalance between alveolar apoptosis and alveolar proliferation in advanced emphysema.

In a study in patients undergoing lobectomy for lung cancer, there was increased apoptosis of alveolar walls by TUNEL assay and increased proliferation of alveolar cells in 10 subjects with emphysema, when compared with lungs from 10 asymptomatic smokers, and 10 nonsmokers (LIU et al. 2009). They also demonstrated increased apoptosis and decreased numbers of Type II epithelial cells in the lungs with emphysema.

As a result of previous studies showing increased apoptosis in human lungs with emphysema (Yokohori et al., 2004), and induction of apoptosis by caspase 3 in mice (Aoshiba et al., 2003), these investigators (Aoshiba & Nagai, 2009) proposed a senescence hypothesis as a pathogenic mechanism in emphysema. They speculated that cellular senescence was the cause of the insufficient cellular proliferation in emphysema, and found that senescence markers were increased in emphysema lungs. They considered that smoking and aging caused alveolar and airway cells to senesce, and senescence decreased tissue repair resulting in reduced cell numbers.

5. Conclusions

Protease-antiprotease imbalance is likely to have a major pathogenic role in the development of emphysema in severe AAT deficiency. However the case in non-AAT deficient smokers is not firmly established, but is supported by several studies showing associations of emphysema with proteolytic enzyme levels or message expression, and by the

association of polymorphisms with decline in lung function. It is also supported by a review of animal models of cigarette smoke-induced COPD, where the opening sentence of the Abstract supports the protease-antiprotease hypothesis of emphysema (Churg, A., et al., 2008). However there are other mechanisms that play a pathogenic role such as oxidants, inflammation, and T lymphocyte induced immunity. Apoptosis is likely to have a significant pathogenic role in emphysema and may be amenable to therapy in the future.

6. Acknowledgements

I thank Andrew Sandford, Allison Wallace, Hong Li, Takeo Ishii, and Selvarani Vimanathan for their collaboration in studies on alveolar macrophage proteases and antiproteases in relation to emphysema.

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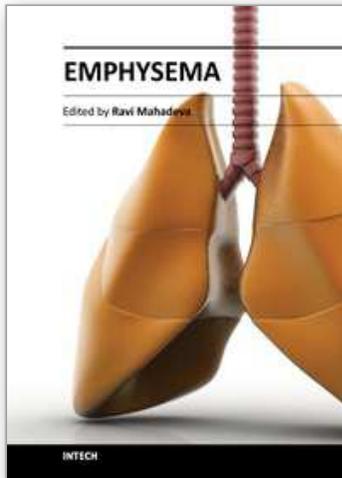
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Emphysema

Edited by Dr. Ravi Mahadeva

ISBN 978-953-51-0433-9

Hard cover, 134 pages

Publisher InTech

Published online 30, March, 2012

Published in print edition March, 2012

Chronic Obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality world-wide. The most common cause is chronic cigarette smoke inhalation which results in a chronic progressive debilitating lung disease with systemic involvement. COPD poses considerable challenges to health care resources, both in the chronic phase and as a result of acute exacerbations which can often require hospital admission. At the current time it is vital that scientific resources are channeled towards understanding the pathogenesis and natural history of the disease, to direct new treatment strategies for rigorous evaluation. This book encompasses some emerging concepts and new treatment modalities which hopefully will lead to better outcomes for this devastating disease.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Raja T. Abboud (2012). Pathogenic Mechanisms in Emphysema: From Protease Anti-Protease Imbalance to Apoptosis, Emphysema, Dr. Ravi Mahadeva (Ed.), ISBN: 978-953-51-0433-9, InTech, Available from: <http://www.intechopen.com/books/emphysema/pathogenic-mechanisms-in-emphysema-from-protease-anti-protease-imbalance-to-apoptosis->

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