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Pathogenesis of COPD. Part I. The role of protease-antiprotease imbalance in emphysema

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SUMMARY

This review covers protease-antiprotease imbalance in the development of emphysema in smokers. This imbalance is likely to play a major pathogenic role in the development of emphysema in subjects with severe α_1-antitrypsin deficiency who smoke because of a deficient antiprotease protection against neutrophil elastase release in the lung. Neutrophil elastase is a potent elastolytic enzyme, and its instillation in the lungs of animals results in emphysema. Smoking attracts neutrophils to the lungs and there is an additional accumulation of neutrophils, because the abnormal antitrypsin polymerizes in the lungs and acts as a chemo-attractant to neutrophils.

In subjects who do not have antitrypsin deficiency, the case for elastolytic injury by neutrophils causing emphysema is less definite, because of the lack of a severe deficiency of active α_1-ntitrypsin leading to unopposed elastolysis by neutrophil elastase. It is likely that alveolar macrophages play a pathogenic role in emphysema; they express potent elastolytic enzymes, cathepsins and matrix metalloproteases (MMPs), which are induced by smoking. The numbers of macrophages are increased in the region of the respiratory bronchiole, where centrilobular emphysema develops in smokers. Macrophage cathepsins are inhibited by an antiprotease cystatin C, while the MMPs are inhibited by the tissue inhibitors of metalloproteases (TIMPs).

Some pro-inflammatory mediators induce release of MMPs from macrophages without inducing increase in TIMPs, leading to possible protease-antiprotease imbalance. Studies of proteases in alveolar macrophages obtained by bronchoalveolar lavage and studies on lung tissue indicate increased protease expression in subjects with chronic obstructive pulmonary disease (COPD) compared to subjects without COPD.

KEY WORDS: emphysema; protease-antiprotease imbalance; neutrophil elastase; matrix metalloproteases; smoking

THE DISCOVERY of severe α_1-antitrypsin deficiency and its association with emphysema,[1] and the induction of emphysema by intratracheal instillation of a proteolytic enzyme in rats,[2] led to the proteolytic hypothesis of emphysema. According to this hypothesis, smoking induces an increased number of neutrophils and macrophages in the lung and the release of proteolytic enzymes from these cells. The released proteases, not fully inhibited by antiproteases, lead to proteolysis of lung connective tissue (more specifically elastin) and emphysema.[3,4] This review will focus on the protease-antiprotease imbalance in the lung as a pathogenic mechanism in emphysema.

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PROTEASE-ANTIPROTEASE IMBALANCE IN SEVERE ANTITRYPSIN DEFICIENCY

There is strong evidence to support this hypothesis as the main pathogenic mechanism in emphysema associated with severe α_1-antitrypsin deficiency, as α_1-antitrypsin is the main inhibitor of neutrophil elastase.

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In this deficiency, anti-elastase protection in the lung interstitium and alveolar space is markedly decreased to about 15–20% of normal levels, similar to the decrease in plasma levels. Neutrophil elastase is a potent elastolytic enzyme and its intra-tracheal injection in experimental animals induces emphysema.[5,6] Moreover, smoking increases the number of neutrophils in the lung and induces the release of neutrophil elastase. Another mechanism leading to a protease-antiprotease imbalance in the lung in severe antitrypsin deficiency (piZZ) is that the abnormal Z antitrypsin polymerizing in the lung acts as a neutrophil chemo-attractant, leading to neutrophil recruitment in the lung.[7,8]

Bronchoalveolar lavage (BAL) from chronic obstructive pulmonary disease (COPD) patients with severe antitrypsin deficiency compared with non-deficient patients[9] showed increased neutrophil counts and a marked decrease in the concentration of α_1-antitrypsin in BAL of antitrypsin-deficient patients, but their BAL was still able to inhibit neutrophil elastase. However, neutrophils migrating through a fibronectin membrane release discrete azurophilic granules causing localized proteolysis of fibronectin, particularly in the presence of antitrypsin-deficient serum compared with normal serum.[10] A pathogenic role for neutrophil elastase in antitrypsin-deficient emphysema is supported by the correlation of increased leucocyte elastase concentration with severity of emphysema.[11]

PROTEASE-ANTIPROTEASE IMBALANCE IN COPD WITHOUT SEVERE ANTITRYPSIN DEFICIENCY

The evidence to support protease-antiprotease imbalance as a pathogenic mechanism in emphysema in smokers without antitrypsin deficiency is less strong than for antitrypsin deficiency because of the lack of definitive evidence of severe antiprotease deficiency allowing unopposed proteolysis in the lung. Smoking may cause a protease-antiprotease imbalance in the lung by reducing the functional activity of α_1-antitrypsin in the lung interstitium and 'alveolar' lining fluid, and by increasing the amount of elastolytic proteases released in the lung. Tobacco smoke was reported to inhibit the anti-elastase activity of α_1-antitrypsin (α_1-protease inhibitor) in BAL from smokers compared with non-smokers.[12,13] Other studies, however, did not confirm this reported degree of inactivation.[14–16]

Potential role of neutrophil elastase in emphysema

Smoking acutely induced the release of neutrophil elastase in BAL[17] and increased plasma neutrophil elastase levels.[18] Alveolar macrophages (AM) may bind and internalize released neutrophil elastase in the lung.[19] Evaluation of BAL in 28 patients with COPD showed that the neutrophil elastase burden in BAL correlated directly and BAL antielastase activity correlated inversely with emphysema assessed by computed tomography (CT) and diffusing capacity, supporting the protease-antiprotease hypothesis.[20] A later study reported increased levels of neutrophil elastase in the AM of smokers with CT scan evidence of emphysema,[21] suggesting neutrophil elastase release in the lung and its uptake by AM. Once neutrophil elastase binds to elastin, the elastase may continue to be active and may not be inhibited by active α_1-antitrypsin in the surrounding medium.[22]

Potential role of macrophage proteases in emphysema

Pathological studies of young smokers dying accidentally reported an increased number of macrophages in the respiratory bronchioles,[23] where centrilobular emphysema develops in smokers without antitrypsin deficiency, suggesting a potential role of macrophages in centrilobular emphysema. Morphometric studies of resected human lungs showed that the extent of emphysema was directly related to the numbers of AM but not neutrophils.[24] Chapman et al. showed that elastolysis by AM in vitro was not inhibited by α_1-antitrypsin, while that of neutrophils was inhibited.[25,26] Several elastolytic enzymes were subsequently demonstrated in human AM: cathepsins L and S,[27–29] the matrix metalloproteases (MMPs) MMP-2 and MMP-9 (previously termed 72 and 92 kDa collagenases or gelatinases A and B, respectively),[30] and MMP-12.[31] In addition, interstitial collagenase, MMP-1, a non-elastolytic enzyme, has been implicated in the pathogenesis of emphysema in transgenic mice expressing MMP-1,[32,33] by degrading type III collagen.[34]

Several studies support a pathogenic role for macrophage proteases in human emphysema. Elastolytic activity of cultured AM from patients with emphysema was increased compared with that of patients with bronchitis or other lung diseases.[35] A study of 34 healthy smokers (mean age 46 years) reported significantly greater AM cell counts in BAL in those with emphysema by CT compared to those without emphysema, suggesting a greater AM elastase load in the lungs, even though AM elastolytic activity/cell was similar.[36] In more recent human studies, AM obtained by BAL from 10 emphysema patients, compared with 10 matched controls, had increased expression of MMP9 and MMP1.[37] 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.[38] A study using immunohistochemistry of lung tissue showed increases in MMP1, MMP2, MMP8 and MMP9 in lung tissue from COPD patients compared with controls.[39] Increased expression of MMP1 was reported in the lungs of patients with emphysema;[40] the MMP1 was localised to the type II epithelial cells but not macrophages.

MMP12 is required for cigarette smoke-induced emphysema in mice; mice homozygous for a knockout of the MMP12 gene, in contrast to controls, did

not show increased macrophages in their lungs and did not develop emphysema in response to cigarette smoke exposure.[41] A human study recently reported that the number of AM in BAL expressing MMP12 and the level of MMP12 expression was higher in COPD patients than in controls.[42]

Several studies have shown that AM elastase mRNA and protein levels are induced by smoking and pro-inflammatory stimuli. Investigators have shown increased expression of cathepsin L in AM from smokers,[43] and also increased activity of cathepsin S in AM lysates from smokers.[28] Studies have also shown increased expression of MMPs by pro-inflammatory mediators, such as the marked increase in mRNA for MMP12 in cultured AM by lipopolysaccharide (LPS).[44] Tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) increased the expression of MMP9 by human macrophages without increasing its inhibitor, TIMP1,[45] indicating the potential for these two mediators, which are increased in COPD, to produce an imbalance between MMP9 and its inhibitor. TNF-α release in mice by cigarette smoke was dependent on MMP-12[46] and was abolished in MMP12 knockout mice; TNF-α accounted for 70% of smoke-induced emphysema in the mouse.[47] AM from patients with COPD released more MMP9 in vitro than AM from healthy smokers, and stimulation by IL-1β, LPS, and cigarette smoke solution increased MMP9 secretion.[48] The same group showed that MMP, cysteine proteases and serine proteases contribute to in vitro elastolysis by human AM during the 72 h evaluation,[49] indicating the difficulty in implicating a specific protease in lung destruction.

An MMP9 promoter polymorphism (C-1562T) was associated with emphysema by CT scan in Japanese smokers,[50] with upper lung emphysema in another Japanese population,[51] and with COPD in a Chinese population.[52]

Additional mechanisms

This review has focused on neutrophil and macrophage proteases, but proteases from other cells such as fibroblasts and epithelial cells may also be involved. Apoptosis (programmed cell death) of alveolar epithelial and endothelial cells and processes related to senescence may also have a pathogenic role in emphysema.[53]

Role of the macrophage protease inhibitors TIMPs and cystatin C 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.[54] AM from COPD patients release less TIMP1 in vitro than those from smokers without COPD and non-smokers. [55] TIMP3 is the only TIMP that binds strongly to the extracellular matrix. TIMP3 knockout mice demonstrate progressive airspace

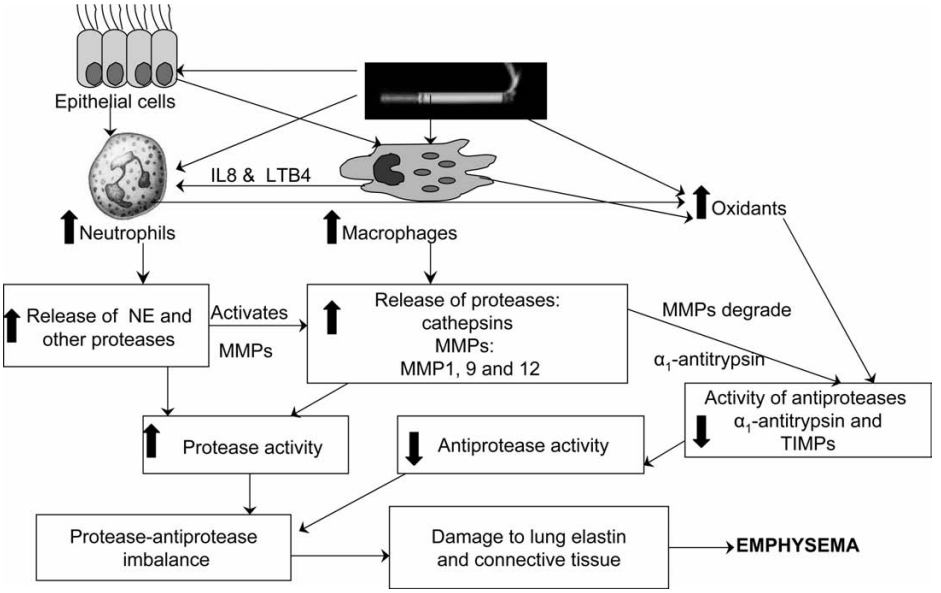

Figure Diagram showing the pathways leading to smoking-induced protease-antiprotease imbalance in the lung. Smoking induces epithelial cells to produce cytokines that stimulate neutrophils and macrophages. Cigarette smoke also acts directly on neutrophils and macrophages to activate them. Cigarette smoke has oxidants that 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. IL = interleukin; LTB = leukotriene B; NE = neutrophil elastase; MMP = matrix metalloproteases; TIMP = tissue inhibitor of metalloproteases; TNF-α = tumor necrosis factor alpha.

Table 1 Evidence supporting proteolysis in human emphysema

Study	Findings	Author, reference
1 BAL in 28 patients with COPD	BAL neutrophil elastase burden correlated directly and anti-elastase activity inversely with emphysema assessed by CT scan and by diffusing capacity	Fujita et al.[20]
2 BAL in 36 older volunteers (mean age 61 years) with evaluation of NE bound to AM	NE esterolytic activity by AM and immunologic NE release by cultured AM, were increased in subjects with CT scan evidence of emphysema compared with those with no emphysema	Betsuyaku et al.[21]
3 BAL and determination of elastolytic activity of cultured AM	Increased elastolytic activity of AM from patients with emphysema compared with patients with bronchitis or other lung diseases	Muley et al.[35]
4 BAL from 10 patients with emphysema compared with matched controls	MMP-1 & MMP-9 expression of AM and collagenase activity of cultured AM were significantly greater in patients with emphysema compared with the controls	Finlay et al.[37]
5 Evaluation of human lung tissue	Emphysematous lung tissue had significantly higher levels of MMP-9 and MMP-2 compared with control lungs, and higher elastolytic activity by zymography corresponding to MMP-2	Ohnishi et al.[38]
6 Evaluation of human lung tissue from 10 COPD patients and 5 controls	Increased MMP-1, MMP-2, MMP-8 (collagenase 2) and MMP-9 in COPD lung tissue	Segura-Valdez et al.[39]
7 Evaluation of human lung tissue from 23 emphysema patients and 8 normal controls	MMP-1 RNA, protein, and activity are present in emphysema lungs but not in normal control lungs or in smokers' lungs without emphysema. In addition, the MMP was localized to type II pneumocytes, not AM	Imai et al.[40]

BAL = bronchoalveolar lavage; COPD = chronic obstructive pulmonary disease; CT = computed tomography; NE = neutrophil elastase; AM = alveolar macrophages; MMP = matrix metalloproteases.

enlargement and enhanced collagen degradation without inflammation or increased elastin breakdown.[56] There are, however, no reported associations between TIMP 3 polymorphisms and COPD. A polymorphism in the TIMP2 gene (G853A) was associated with COPD in a Japanese[57] and an Egyptian population.[58]

Cystatin C is present in most biological fluids and is a potent inhibitor of cathepsins. Cystatin C is a major product of AM[59] and is secreted by AM from smokers at higher levels than non-smokers.[60] The concentrations of cathepsin L and its inhibitor cystatin C were both significantly increased in BAL fluid from

Table 2 Proteolytic mechanisms in experimental emphysema

Experiment	Results	Author, reference
1 Transgenic mice expressing human collagenase (MMP-1)	Developed lesions resembling human emphysema. The 1992 paper first implicated MMP-1, a non-elastolytic collagenase, in emphysema. This was confirmed in 2003 by the same investigator; mice over-expressing MMP-1 after birth developed adult-onset emphysema	D'Armiento et al.[32] Foronjy et al.[33]
2 MMP-12 knockout mice vs. control mice exposed to cigarette smoke	MMP-12 knockouts did not develop emphysema and did not have increased number of macrophages following smoke exposure	Hautamaki et al.[41]
3 Over-expression of IFN-γ in mice, and over-expression of IL-13 in mice	Led to emphysema with induction of MMP-12 and MMP-9, and cathepsins, indicating a pathogenic potential for both groups of proteases in emphysema	Wang et al. [62] Zheng et al. [63]
4 Mice with knockout of TIMP-3 (the only TIMP residing in the extracellular matrix)	Developed spontaneous air space enlargement in the lung 2 weeks after birth, which progressed with age Lungs from aged null animals showed reduced collagen, increased MMP activity, supporting an imbalance between MMPs and TIMPs in pathogenesis of emphysema	Leco et al.[56]
5 Mice with knockout of MMP-12, and control mice exposed to cigarette smoke	MMP-12 knockouts failed to release TNF-α and lacked an inflammatory responses to cigarette smoke, indicating that MMP-12 mediated TNF-α release	Churg et al.[46]
TNF-α knockout mice and control mice exposed to cigarette smoke over 6 months	TNF-α knockout mice had 70% less emphysema than control mice, indicating that TNF-α is responsible for about 70% of smoke-induced emphysema in mice	Churg et al.[47]
6 Guinea pigs exposed to cigarette smoke; half received MMP inhibitor	Cigarette smoke led to emphysematous lesions, increased MMP-1 and MMP-9 activities. MMP inhibition attenuated smoke-induced emphysema	Selman et al.[64]
7 NE knockout vs. control mice exposed to long-term cigarette smoke	NE knockouts showed 59% protection from emphysema, indicating that NE contributes to smoke-induced emphysema in mice.	Shapiro et al.[65]

MMP = matrix metalloproteases; IFN-γ = interferon-gamma; IL = interleukin; TIMP = tissue inhibitor of metalloproteases; TNF = tumour necrosis factor; NE = neutrophil elastase.

smokers with emphysema compared with those without emphysema; however, there was no significant difference in cathepsin L activity in BAL between the two groups.[61]

CONCLUSION

Protease-antiprotease imbalance is likely to have an important pathogenic role in the development of emphysema in COPD. The Figure shows interacting mechanisms induced by smoking and leading to protease-antiprotease imbalance. Tables 1 and 2 summarize human studies and animal experiments supporting protease-antiprotease imbalance in the pathogenesis of emphysema.

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RÉSUMÉ

Cette revue concerne le rôle du déséquilibre protéase/antiprotéase dans l'apparition de l'emphysème chez les fumeurs. Ce déséquilibre est susceptible de jouer un rôle pathogène majeur dans le développement de l'emphysème chez les sujets fumeurs atteints de déficience grave de l'α_1-antitrypsine en raison de la déficience de la protection par l'antiprotéase contre l'élastase des neutrophiles libérée dans le poumon. L'élastase des neutrophiles est

un puissant enzyme élastolytique et son instillation dans les poumons d'animaux entraîne l'emphysème. Le fait de fumer attire les neutrophiles dans le poumon et une accumulation supplémentaire de neutrophiles survient à cause de la polymérisation de l'antitrypsine anormale dans les poumons ; celle-ci est chimiotactique pour les neutrophiles.

Chez les sujets sans déficience en antitrypsine, le problème du rôle d'une agression élastolytique par les neutrophiles comme cause de l'emphysème est moins claire en raison de l'absence d'une déficience sévère en l'α_1-antitrypsine active conduisant sans son opposition à une élastolyse par l'élastase neutrophilique. Il est probable que les macrophages alvéolaires jouent un rôle pathogène dans l'emphysème ; ils libèrent de puissants enzymes élastolytiques, des cathepsines et des métalloprotéases de la matrice (MMP) qui sont stimulés par le fait de fumer. Les nombres de macrophages sont accrus dans la région des bronchioles respiratoires où chez les fumeurs on voit se développer un emphysème centrilobulaire. Les cathepsines des macrophages sont inhibées par une cystatine C antiprotéase, alors que les MMP sont inhibées par les inhibiteurs tissulaires des métalloprotéases (TIMP).

Certains médiateurs pro-inflammatoires libèrent les MMP des macrophages sans induire une augmentation des TIMP, ce qui conduit à la possibilité d'un déséquilibre protease/antiprotéase. Des études des protéases dans les macrophages alvéolaires obtenues par lavage bronchoalvéolaire et des études sur le tissu pulmonaire indiquent une expression accrue des protéases chez les sujets atteints de bronchopneumathies chroniques obstructives (BPCO) par comparaison avec les sujets sans BPCO.

RESUMEN

El presente artículo analiza el desequilibrio entre proteasas y antiproteasas en la aparición de enfisema en los fumadores. Este desequilibrio puede tener un importante rol patógeno en la aparición de enfisema en personas con grave deficiencia de α_1-antitripsina que fuman, a causa de una inadecuada protección de la antiproteasa contra la elastasa liberada por los neutrófilos en el pulmón. La elastasa de los neutrófilos es una potente enzima elastolítica y su instilación en los pulmones provoca enfisema en animales. El tabaquismo atrae neutrófilos al pulmón y ocurre además una acumulación de los mismos, pues la antitripsina anormal se polimeriza en el pulmón y actúa como un factor quimiotáctico de neutrófilos.

En personas sin deficiencia de antitripsina, la función de la lesión elastolítica de los neutrófilos en el origen del enfisema es menos clara, pues no se da la deficiencia grave de α_1-antitripsina activa que deje sin contrarresto la acción de la elastasa neutrofílica. Es probable que los macrófagos alveolares cumplan una función patógena en el enfisema, pues expresan potentes enzimas elastolíticas, catepsina y metaloproteasas de matriz (MMP), inducidas por el tabaquismo. La cantidad de macrófagos se encuentra aumentada en la región del bronquiolo respiratorio, donde se presenta el enfisema centrolobulillar en los fumadores. Las catepsinas de los macrófagos son inhibidas por la antiproteasa cistatina C y las MMP por los inhibidores de metaloproteasas de los tejidos (TIMP).

Algunos mediadores proinflamatorios inducen la liberación de MMP por los macrófagos, sin provocar un aumento de los TIMP, dando origen a un posible desequilibrio entre proteasas y antiproteasas. Los estudios sobre las proteasas en los macrófagos alveolares obtenidos por lavado broncoalveolar y los estudios en tejidos pulmonares indican una expresión aumentada de las proteasas en individuos con enfermedad pulmonar obstructiva crónica, cuando se comparan con individuos sin esta enfermedad.