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Perspective

Emphysema: the challenge of the remodelled lung

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Abstract

Emphysema is recognized as the component of chronic obstructive airways disease that is responsible for airways obstruction. Different patterns of emphysema are, however, recognized, suggesting possible different pathogenetic processes within the lung. This, coupled with the associated idea of susceptibility factors to the development of emphysema, has led to studies of genes that may be involved in the defence of the lung from proteolytic and oxidative damage. These studies have been driven by the goal of finding a treatment for emphysema, but appear to have lost sight of the fundamental remodelling of the lung that has occurred in patients with emphysema and the fact that it is not a single morphological entity. Copyright © 2004 John Wiley & Sons, Ltd.

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Historical background

Emphysema, as a major component of chronic obstructive pulmonary disease (COPD), is a significant cause of morbidity and mortality, although perhaps only a quarter of smokers develop clinically significant emphysema [1]. The presence and severity of emphysema in patients with COPD, whether assessed microscopically or by computed tomography (CT), has been shown to correlate with decreased gas transfer and the fall in FEV_1 [2] that characterizes this condition and it is believed to be the pathological cause of the fixed irreversible airways obstruction seen in these individuals due to loss of alveolar wall attachments to small bronchioles in the distal lung [3,4].

Emphysema was first defined as 'a condition of the lung characterized by an increase beyond the normal in size of the airspaces distal to the terminal bronchiole either from dilation or from destruction of their walls' [5]. This original definition did not distinguish between over-inflation and the disruption of the lung architecture, which occurs in smoking-related emphysema. In 1962, the definition suggested was 'a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchioli accompanied by destruction of their walls' [6]. This was further modified in 1985, by adding 'accompanied by destruction of their walls and without obvious fibrosis' [7].

Whilst useful, these definitions are actually an oversimplification. To fulfil the definition of emphysema, three points must be taken into account, ie the size of airspace, evidence for a destructive process, and an assessment that fibrosis is minimal [8]. None of the definitions was accompanied by criteria that allowed the concept of 'normal airspace size' to be defined. Similarly, in the 1985 definition, the term 'without obvious fibrosis' is clearly a conceptual statement and may give rise to problems in relationship to the presence of smoking-related fibrosis in lungs where both inflammatory cells and fibrosis are frequently encountered. Furthermore, changes occur in ageing lungs [9] that are qualitatively similar to emphysema in smokers, suggesting either that clinically significant emphysema is at the severe end of normal tissue loss through ageing (similar to bone and neurones) or that ageing-related loss of lung tissue is the benign end of a spectrum of disease resulting from environmental exposure to toxic chemicals [10].

The pathological appearances of the lungs in patients with COPD are well described in pathology textbooks [11] and for several decades emphysema has essentially been a pathologist's territory, with great effort being directed towards classification into anatomic types. Thus, centriacinar emphysema (CAE) (synonyms preacinar, proximal acinar, centrilobular) was envisaged as the result of immediate injury to respiratory bronchioles and adjacent tissues, essentially an active destructive process. The abnormal airspaces are found in association with respiratory bronchioles, though in more severe cases virtually the whole acinar unit may be involved. In most cases of CAE, there is a distinct distribution with gradation of severity from the apex of the lung towards the base. Panacinar emphysema (PAE) (synonyms periacinar, distal acinar), by contrast, is a more diffuse process, at least in its early stages, characterized by remodelling of the lung, loss of elastic recoil, and increased capacity. Abnormally large airspaces are found evenly distributed across the acinar unit. Adjacent acinar units are usually involved to a similar degree, giving a confluent appearance to the cut surface of the lung, with extensive areas being

involved. There is no obvious macroscopic pattern to the distribution of the disease in the lung. In paraseptal emphysema, the abnormal airspaces run along the edge of the acinar unit, but only where it abuts against a fixed structure such as the pleura, a vessel or a septum. Two other types of emphysematous changes were described, scar emphysema (synonym irregular), where the emphysematous spaces are found around the margins of a scar, and bullous emphysema, in which areas of emphysema are locally overdistended to produce a lesion which, if superficial, stands proud of the pleural surface [12].

These differences, with the associated implication that the aetiology and pathogenesis may differ, have been largely forgotten by researchers because no reliable functional or clinically significant differences have been identified that correlate with structure. Patients with COPD do vary in their clinical behaviour and patterns of respiratory failure, but no relationship between these and the pattern of emphysema present has been demonstrable [13]. Nor has any link between any of the recognized risk factors for emphysema and the pattern of disease been identified. Thus, the term 'emphysema' has passed into common usage as if it is a homogeneous disease.

Possible aetiology and pathogenesis

The absence of any association with risk factors or clinical features does, however, raise the possibility that the development of emphysema and its different pathological patterns could be the result of interaction between external risk factors and intrinsic host susceptibility factors. The concept of susceptibility factors was first suggested by the observation that emphysema occurs in patients with α_1-anti-trypsin (α_1-AT) deficiency [14] and that this was exacerbated by concomitant smoking. α_1-AT is a major plasma inhibitor of proteolytic enzymes and since such enzymes can induce experimental 'emphysema' in animal models, it seemed plausable that the association of α-protease deficiency with emphysema [15] was the result of unopposed proteolytic activity in the lung giving rise to the generally accepted protease/anti-protease theory of injury. This was further refined when the enzyme elastin was also found to have the potential to cause experimental 'emphysema'. Thus, the protease/anti-protease theory was evolved into the elastase/anti-elastase theory of the pathogenesis of emphysema, with neutrophil elastase (NE) being the major enzyme implicated [16–19]. Macrophages are another potential source of protease enzymes and are commonly seen in a centriacinar position in smokers, although not always concomitant with emphysema [20]. It has been postulated that these cells, possibly regulated by T-lymphocytes, release macrophage serine elastase, which is much more efficient in degrading lung interstitium, and that this may be more important [21].

Whilst clearly applicable to animal models and the human situation in α_1-AT deficiency, this theory has not been fully substantiated for the generality of human emphysema. Refinement of the theory has therefore occurred, in particular recognizing the role of oxidants. Each puff of cigarette smoke generates 10^{15}–10^{17} free radicals [22,23]. In addition, oxidative metabolism of other compounds in both bronchiolar and alveolar epithelium, especially by smoke-inducible cytochrome p450's, generates even more radicals [23,24]. Oxygen free radicals damage many structures and cause immediate neutrophilic infiltration, as well as directly inhibiting protease inhibitors [25]. In addition, nicotine may prolong the life span of neutrophils and thus potentiate lung damage [26]. So, the theory of protease/anti-protease imbalance has been modified by adding the effects of oxidants and possibly by invoking different elements of both innate and adaptive immunity.

There still remains, however, the question of why only a proportion of smokers develop emphysema. Within the extracellular fluid in the lung, there is a bias towards the quenching of oxidants and free radicals. Uric acid, reduced glutathione, ascorbate, sacrificial sulphoproteins which can be oxidized and discarded, extracellular superoxide dismutase (SOD3), catalase, and glutathione peroxidase all serve to protect the epithelial lining. Within the cells, in addition, there are protective antioxidant enzymes that by conjugation, cleavage of peroxides or deapoxidation remove toxic species [27]. Could differences in this antioxidant protection be important in determining whether or not emphysema occurs?

Oxidative stress: the balancing act

A number of enzymes involved in the activation, metabolism, and detoxification of cigarette components are polymorphic. In some situations, this genotypic variation is reflected by a difference in functional enzyme activity. The range of enzymes is large, substrate specificity frequently overlaps, and there may be considerable redundancy between different enzymes.

Cytochrome p450 1A1 (CYP1A1) has a rare variant (<5%) which is thought to result in increased inducibility and hence activity of the enzyme. CYP1A1 metabolizes many components of cigarette smoke to active radicals and the enzyme is itself induced by cigarette smoke [28]. Several studies have linked the rare variant of CYP1A1 genotype to increased susceptibility to lung cancer in smokers. However, these studies highlight one of the problems inherent in studies of emphysema and lung cancer, namely that both diseases may co-exist. A similar study repeated in a UK population where the presence of emphysema and cancer was taken into consideration revealed a very small association between CYP1A1 genotype and susceptibility to emphysema, but not to cancer. However,

the relative risk was small and of doubtful significance in the population as a whole [29].

Similarly, a detoxification enzyme, glutathione S-transferase M1 (GSTM1), a member of a detoxification family conjugating free radical species to reduce glutathione and also directly engaged in protection against peroxidation injury, is polymorphic [30]. Approximately 50% of the population have a deletion of part of or the entire gene at both alleles and are therefore GSTM1 null [31]. Again, several studies have associated GSTM1 null with increased risk of lung cancer, but once again if the presence or absence of emphysema is taken into account, the association is with emphysema rather than lung cancer [32]. Although GSTM1 is expressed in lung, it is present at a higher concentration in liver, raising the possibility that much injury inflicted on the lung by cigarette smoke may be the result of systemic metabolism.

Microsomal epoxide hydrolase (mEPHX) is an enzyme involved in the metabolism of highly reactive epoxide intermediates. Four distinct mEPHX alleles exist which arise because of the presence of two point mutations in the gene. An exon 3 T-to-C mutation changes Tyr 113 to His, reducing enzyme activity by at least 50% (slow allele). The second, an A-to-G transition mutation in exon 4 of the gene, changes His 139 to Arg, producing an enzyme with a putative increase in activity of at least 25% (fast allele). The wild-type allele is characterized by the absence of these two changes, but the presence of both mutations in a rare mEPHX allele produces a hydrolase with normal activity. It has been demonstrated that there is an association between genetically defined polymorphisms in mEPHX activity and susceptibility to COPD and emphysema and this suggests that highly reactive epoxide intermediates may play a role in the initiation and progression of the character tissue abnormalities seen in emphysema [33]. Polymorphisms of the mEPHX gene may be an important risk factor in lung disease associated with oxidative stress, consistent with the direct effects of cigarette smoke components.

We appear to have come some distance in understanding the external environmental factors that lead to emphysema and possible genetic risk factors that may influence who develops it. One of the challenges, however, in further understanding the role and interaction of these factors will be in explaining the divergent patterns of lung remodelling that occur in these patients which, as described, is not homogeneous.

Implications for treatment

Much of the interest in this type of research in the last few years has been driven by an interest in developing strategies or agents that might interfere with these proposed pathogenetic mechanisms. So, what are the implications for the treatment of emphysema from this research? What is clear is that the most effective preventative measure to reduce the incidence of emphysema is for people not to smoke cigarettes, or to stop if they do smoke [1]. The disease is slowly progressive and there is evidence that the rate of loss of lung tissue reduces to 'normal levels' if cigarette smoking is stopped [34]. It remains unclear, however, whether approaches based on modulating inflammation or modulating the oxidant/antioxidant balance will be feasible.

Techniques under evaluation include the use of exogenously administered pharmacological agents, but also gene therapy with the aim of local production of anti-elastase/elastase inhibitors in the treated lung [35–39]. There still remains the problem, so far ignored, that the pathological basis of emphysema and fixed airways obstruction is the result of lung remodelling with the loss of alveolar walls and support of the small peripheral bronchioles. All the proposed treatments are, at most, likely to prevent or modify future remodelling in patients who continue to smoke, but it would seem unlikely that even with stem cell therapy (for discussion see ref 40) lost alveolar tissue will be restored. In many respects, a more realistic, simpler, and cheaper alternative for the vast majority of patients with emphysema is to prevent disease progression by smoking cessation. The alternative approach, which appears to be where we may be heading, is the development of agents which at best will protect the lung from damage, whilst permitting the patient to continue smoking!

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