

Review article

Lung collagen: more than scaffolding

Collagens of various types are the major group of proteins in the lung. They are present in all major structures, including airways, blood vessels, the interstitium of the lung parenchyma, and the basement membranes of epithelial and endothelial cells. Any alterations in quantity, structure, or the geometry of their distribution would be likely to alter lung function. Changes would have particularly dramatic effects if they occurred in the interstitium, where the distance between air and blood may be as little as 50 nm.¹

A collagen molecule typically has a rod like structure, 300 nm in length and 3 nm in diameter, forming tightly packed fibrils with diameters up to about 100 nm. Any large deposits of collagen or collagen deposition with incorrect orientation within the interstitium may severely impede gas exchange; while loss of collagen from the interstitium would lead to disruption of the normal alveolar network, and loss from basement membranes would compromise their role controlling entry of materials to and from cells in the lung. Not surprisingly perhaps against this background, lung diseases occur in which imbalances in collagen structure or metabolism appear to play a part. This editorial review describes some of the developments in our understanding of lung collagen and its role in pulmonary disease. Particular attention will

be given to its role in two disorders: pulmonary fibrosis and emphysema.

Collagen structure and metabolism

This section offers a brief summary of what is currently known about the structure and metabolism of collagen. Readers are referred elsewhere for more detailed reviews of collagen biochemistry.²⁻⁵ An appreciation of the pathways described here may be useful for an understanding of what follows, but some readers may wish to pass directly to the next section on lung collagen.

Our perception of collagen has changed dramatically over the last 10 years. One of the major breakthroughs has been the discovery of collagen isotypes and the recognition that there is a family of collagens—each having distinctive structural and metabolic characteristics, and in some cases different functions. There are thought to be at least 11 different collagens, coded by a group of about 20 genes⁶ (table). Each of these so called collagen types comprises three polypeptide chains (α chains), which intertwine in a right handed triple helix. The individual chains typically contain about 1000 amino acids, and a characteristic of all of them is a high proportion of glycine, proline, and hydroxyproline residues. A large proportion of the polypeptide chain contains repeat units of the structure Gly-X-Y, where X and Y are either proline, alanine, or hydroxyproline. It is likely

Address for reprint requests: Dr Geoffrey J Laurent, Lung Biochemistry Unit, Department of Thoracic Medicine, Cardiothoracic Institute, London SW3 6HP.

Collagen types and their likely distribution in the lung

Type	Likely distribution in the lung	Molecular structure	Likely cells responsible for bulk of reproduction
I	Large bronchi, blood vessels, interstitium	$[\alpha_1(I)]_2\alpha_2(I)$	Fibroblasts
I (trimer)	Presence in lung uncertain	$[\alpha_1(I)]_3$	Fibroblasts
II	Bronchial and tracheal cartilage	$[\alpha_1(II)]_3$	Chondrocytes
III	Large bronchi, blood vessels, interstitium	$[\alpha_1(III)]_3$	Fibroblasts
IV	Basement membranes	$[\alpha_1(IV)]_2\alpha_2(IV)$	Endothelial and epithelial cells
V	Basement membranes and interstitium	$\alpha_1(V)\alpha_2(V)\alpha_3(V)$ Structure uncertain, may be comprised of 3 distinct molecules	Fibroblasts
VI	Blood vessels and interstitium codistributing with types I and III collagen	$\alpha_1(VI)\alpha_2(VI)\alpha_3(VI)$	Fibroblasts
VII	Uncertain	$[\alpha_1(VII)]_3$	Uncertain
VIII	Uncertain	Uncertain	Endothelial cells
IX	Cartilage	$\alpha_1(IX)\alpha_2(IX)\alpha_3(IX)$	Chondrocytes
X	Cartilage	$[\alpha_1(X)]_3$	Chondrocytes
XI	Cartilage	Uncertain	Chondrocytes

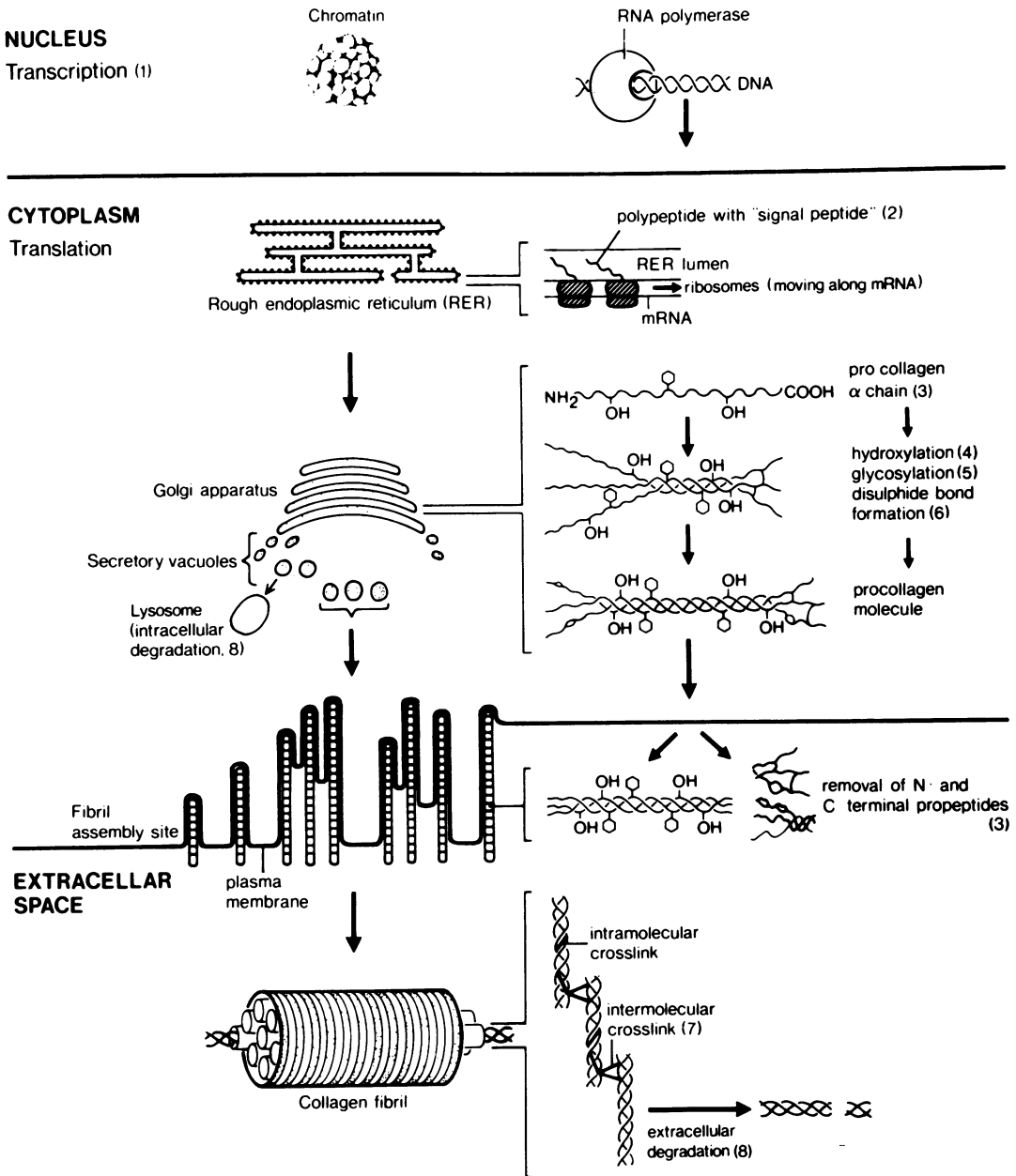


Fig 1 Likely steps in the pathway of lung collagen synthesis and degradation.

that all the collagens that are currently well described will be found in the lung, either in the parenchyma or in the higher airways. They are listed in the table and discussed in more detail later.

In addition to these advances in the appreciation of the diversity of collagen structure, there have been

major developments in our understanding of the pathways of collagen metabolism and the extensive processing that occurs at intracellular and extracellular sites. These include the following steps, many of which are illustrated in figure 1, with numbered cross references to this text.

1 Extensive processing of the messenger RNA for collagen

The gene for the $\alpha_2(I)$ chain of type I collagen contains many more bases than are required to code for the polypeptide. The coding sequences (exons) are interspersed throughout the gene, separated by about 50 intervening sequences (introns). During processing within the nucleus these sequences must be specifically excised and the strands, subsequently ligated before transcription to the mRNA in the endoplasmic reticulum (fig 1).

2 Synthesis with "signal" sequence

The initial transcript (pre-procollagen) has a short sequence of amino acids at one end of the molecule. This sequence of predominantly hydrophobic amino acids functions to direct the molecule into the Golgi apparatus, from which it is destined to be secreted from the cell.

3 Collagen synthesised in a precursor form

After removal of the "signal" sequence, the polypeptide is still considerably longer than the chain that eventually forms fibrils in the extracellular matrix. There are peptide extensions at both ends of the molecule (referred to as procollagen peptides), which do not contain long repeat structures of the Gly-X-Y form and, apart from one short section, do not form a triple helix. These extensions may have several functions: promoting formation of the triple helix, preventing premature fibril formation, and influencing extracellular fibril formation. Possibly they also have a role in the control of collagen production, with the *N* terminal propeptide exerting a negative feedback on procollagen synthesis. The peptides are removed by specific amino and carboxyproteases, which are thought to act either at the membrane just before secretion or some time after secretion from the cell, depending on the collagen type.

4 Hydroxylation of proline and lysine

About one half of the proline residues in the procollagen chain are hydroxylated after production of the molecule. There are specific enzymes (3- and 4-prolyl hydroxylases) requiring as cofactors molecular oxygen, iron, ascorbic acid, and α ketoglutaric acid. Another hydroxylase (lysyl hydroxylase) is responsible for the hydroxylation of lysine residues.

Hydroxyproline is also found in some other proteins (elastin, acetylcholinesterase, the Clq components of complement, and a component of surfactant); but in quantitative terms this is insignificant. This hydroxylation of proline is used as the basis for the quantitation of lung collagen.

5 Addition of carbohydrate moieties to the polypeptide chains

Carbohydrates, mostly glucose and galactose residues, are covalently bonded to hydroxylysine in reactions requiring the enzymes galactosyl transferase and glucosyl transferase. The extent of glycosylation varies greatly for the different collagens; it is particularly high in type IV collagen, where these carbohydrate moieties represent as much as 10% by weight of the molecules.

6 Disulphide bonding between α chains

For all collagens except type I disulphide bonds are formed between cysteine residues of adjacent chains, as well as interchain links between adjacent molecules.

7 Formation of covalent cross linked compounds between amino acids side chains

After the modifications described above, most of which take place in the Golgi apparatus, procollagen molecules are secreted from cells via the secretory vacuoles (see fig 1). After removal of the propeptides, collagens are assembled into fibrils in recesses of the fibroblast plasma membrane. These fibrils are not stabilised until covalent cross links form between chains of adjacent molecules. The first step in this process is the modification of the lysine and hydroxylysine residues in reactions requiring the copper dependent enzyme lysyl oxidase. Cross linking then occurs via reactions between these products and unmodified lysine or hydroxylysine chains.

8 Degradation of procollagen and collagen

Another recent development, discussed in detail later, is the finding that collagen turnover (synthesis and degradation) is more rapid in normal tissues than was originally believed. For this reason pathways of degradation, which are still relatively poorly understood, are potentially important sites for regulation of collagen homeostasis. The pathways of collagen degradation are complex and there are various sites, both intracellular and extracellular, where breakdown may occur. Once it leaves the cell, the molecule ages chemically with the formation of cross links that render it less susceptible to degradation. In contrast, the procollagen molecule appears to be highly susceptible and a large proportion of newly synthesized molecules may be degraded within minutes of synthesis, before secretion from the cell.

The major pathway for degradation of extracellular collagen appears to depend on collagenases. There are various collagenases that are capable of degrading one or more of the isotypes. The best characterised of these, first isolated from mammalian skin, is capable of degrading all the interstitial collagens

(types I, II, and III) but not, so far as we know, the other types. Degradation occurs in a site specific way, the protease cleaving the chain of the mature triple helix at a peptide bond about three quarters of the way from one end. Once this occurs the molecule becomes susceptible to various other proteases, which may act extracellularly (at neutral pH), or alternatively the denatured chains may be taken up by cells during endocytosis and the chain degraded intracellularly (probably in lysosomes). Collagenase is produced as an inactive proenzyme and is converted to the active form by several proteases, including plasmin and trypsin. Several agents are capable of initiating this conversion (including prostaglandins and cyclic AMP) and at least two antiproteases can act as collagenase inhibitors—they are β_1 anticollagenase and α_2 macroglobulin. Both these compounds are found in plasma and would normally bind any collagenase in serum. The collagenase described above is known to be produced by fibroblasts and is probably prominent in normal collagen turnover. Other collagenases may be important during disease. Macrophages can produce a metalloprotease that is capable of degrading types IV and V collagen. Neutrophils can produce two proteases; one is specific for type IV collagen and the other degrades type III collagen as well as elastin.

Collagen in the normal lung

Collagens of the various types constitute about 15% of the dry weight of human lung tissue and are the major protein group. Several groups of workers have isolated collagens from lung⁷⁻⁹ and examined their distribution with immunohistochemical techniques.⁹⁻¹³ Types I and III are the most abundant of the lung collagens and are present in a ratio of about 2:1,¹⁴⁻¹⁶ codistributing in airways and blood vessels as well as in the interstitium. The molecular structure and distribution of these and other collagen types in lung are summarised in the table.

Comparatively little is known of the rates of collagen metabolism in normal lung. Formerly the prevailing view was that lung collagen, like collagen in other tissues, was either inert or turned over extremely slowly.^{17,18} More recent studies, however, using improved techniques have suggested that synthesis and degradation rates may be quite rapid. In adult rats and rabbits the turnover rate is about 10% a day, implying that amounts of collagen equivalent to one tenth of the total pool are being synthesised and degraded each day. Furthermore, studies of the kinetics of this process *in vivo*¹⁹ and *in vitro*²⁰ have indicated that about 30% of lung collagen is being degraded intracellularly within minutes of its synthesis, before secretion from cells. In contrast, the rate

of breakdown for extracellular collagen is certainly much slower, and possibly highly cross linked collagen does not turn over under normal circumstances.

The implications of these studies are that fibroblasts are not quiescent cells that are stimulated to produce collagen only in disease; rather, they are continually synthesising collagen and may be responsible for its degradation intracellularly and extracellularly. Furthermore, changes in either synthesis or degradation could potentially play a major part in the regulation of collagen mass in lung disease (fig 2). The ways in which these processes are regulated are still poorly understood; clearly, however, there are many potential points for regulation (figs 1 and 2) and recently a host of mediators have been described that can, for cells in culture at least, influence rates at which collagen is synthesised and degraded. Many of these mediators are derived from the cells of the immune and reticuloendothelial system and for that reason there has been much conjecture about their role in diseases where rates of connective tissue protein metabolism are believed to alter.

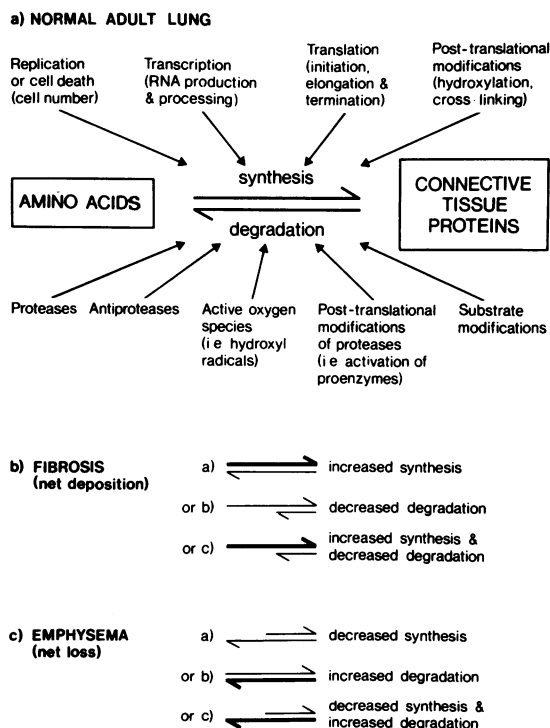


Fig 2 Collagen metabolism in the normal lung and possible changes during pulmonary fibrosis and emphysema.

Collagen in lung disease

The human lung may be exposed to many toxins—particularly those derived from cigarette smoke, but also many other environmental agents. Minor episodes of lung damage are likely to occur continuously, and to be met by the “repair cascade,” eventually leading to collagen deposition in scar tissue. Once the causative agent is no longer present this deposited collagen is likely to be broken down in the “resolution pathway”. The important point, however, is that there has to be a tight balance between synthesis and degradation of connective tissue proteins. Two common disorders of the lung where an imbalance of connective tissue protein metabolism occurs are pulmonary fibrosis and emphysema.

Collagen content and metabolism in pulmonary fibrosis

Pulmonary fibrosis is a general term to describe those disorders for which there is histological evidence of diffuse thickening of alveolar walls. Characteristically fibrous tissue, believed to consist mostly of collagen, is localised predominantly in the interstitium, where gas exchange occurs. Histologists have for some time reported an increase in collagen deposition, although biochemical evidence for this has been controversial. An initial study of lung biopsy samples from patients with idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) suggested no change in collagen concentration or synthesis rates.²¹ The severe limitations inherent in studies of biopsy samples are, however, now well recognised. Briefly, studies of biopsy material demand that collagen content should be expressed with respect to some other constituent, and DNA content has been used most commonly. Histological studies have established that there is a considerable cellular infiltrate during fibrosis, which increases the wet and dry weight as well as the DNA content of the tissue. The histological appearance and collagen concentrations also vary considerably with the site of the biopsy, and the degree of fibrosis (assessed histologically or biochemically) is known to vary with the stage of the disease (see ref 22 for full discussion).

Studies of acute lung disease in man^{23 24} and of experimentally induced fibrosis^{15 25–27} have shown appreciable and extremely rapid increases in total lung collagen, although changes in collagen concentrations were not always apparent. In addition, a recent study of a larger series of patients with pulmonary fibrosis showed a considerable increase in total lung collagen with appreciable increases in collagen concentration.²² Furthermore, the collagen concentration was shown to be greater in postmortem lung samples than in biopsy samples,²² supporting

the notion that collagen deposition is progressive and increases with advancement of the disease.

Studies of collagen metabolism have also been controversial. There is widespread agreement that synthesis rates are increased in experimentally induced fibrosis, but in man this has not yet been demonstrated biochemically. One early study *in vitro*, which examined uptake of radiolabelled proline into the hydroxyproline of biopsy samples obtained from patients with pulmonary fibrosis, suggested that synthesis was no different from the synthesis in control material.²¹ A similar result has been reported by Selman and coworkers,²⁸ who studied a quite large group of patients. Again the major problem relates to the way synthesis is expressed. In both the above studies rates have been expressed with respect to concentration of DNA and therefore an influx of inflammatory cells may mask increases in collagen synthesis rates. This seems likely since studies in experimental animals have shown increased synthesis in terms of fractional rate (that is, with respect to the total collagen pool) but no change when synthesis was related to DNA concentration.²⁹ The inherent limitations of *in vitro* studies have also been questioned since the rates of synthesis obtained for sliced tissue preparations appear to be an order of magnitude lower than those obtained *in vivo*.³⁰ Indirect evidence suggesting an increased synthesis rate in man has come from studies of the enzymes of collagen synthesis and the production of procollagen peptide (see previous section on collagen structure and metabolism). Increased levels of type III procollagen peptide have been reported in serum³¹ and lavage fluid,³² and increased serum levels of glucosyl transferase have also been observed for patients with fibrosing lung disorders.³³

In contrast, there are few studies of collagen degradation during fibrosis. This pathway may be important in the light of recent observations suggesting that collagen turnover in the adult lung is more rapid than was traditionally believed.^{29 30} On the basis of the appearance of labelled hydroxyproline after administration of labelled proline *in vivo*, a decreased degradation of newly synthesised collagen has been suggested for rabbits with bleomycin induced fibrosis.²⁹ There are less data on this in man, although one study of collagenase activity in biopsy samples from patients with pulmonary fibrosis suggested decreased collagenase mediated degradation.²⁸ This contrasts with a report of increased collagenase activity in lavage fluid derived from patients with pulmonary fibrosis,³⁴ although whether this reflects changes in the interstitium is uncertain. Studies such as these highlight the importance of considering degradation as well as synthesis in understanding the mechanisms leading to pulmonary fibrosis (fig 2).

Collagen types in pulmonary fibrosis

There has been considerable interest in the role of changes in collagen types in fibrosis. It has been suggested that shifts to excessive type I collagen with a more fibrillar, rigid structure may lead to impaired gas exchange and some of the physiological characteristics of fibrosis. An early study of collagen types reported an increase in the amount of type I collagen relative to type III in postmortem samples from patients with idiopathic pulmonary fibrosis,¹⁴ and this has been confirmed in both acute³⁵ and chronic³⁶ forms of this disease.

A somewhat different picture has emerged from studies of biopsy samples. Bateman *et al.*,¹⁰ using immunohistochemical methods, suggested a relationship between the presence of type III collagen and disease activity. Kirk *et al.*³⁶ developed biochemical procedures for examining biopsy samples and, although a wide range of values was seen, several patients had type III to type I ratios greater than were seen in either controls or postmortem samples. In addition, patients in the earlier stages of disease also tended to have a greater proportion of type III collagen, as was suggested by immunohistochemical studies.^{13 37} Further, there was a relationship between the relative proportions of these collagen types and response to treatment, implying that biochemical measurements of collagen types might be useful in staging fibrosis.³⁶ To examine these issues further Kirk and colleagues measured the concentration of the type III procollagen peptide (fig 1) in serum of patients with pulmonary fibrosis.³¹ The concentration of this peptide in the serum was higher in patients than in controls and there was a correlation between serum concentrations and the results of type III measurement in lung biopsy samples. Furthermore, patients with the highest concentration of peptide tended to show a better response to steroid treatment, and this response was associated with a decrease in serum peptide concentration. From what we know of the pathway of collagen metabolism these results suggest that synthesis may be increased in fibrosis and that treatment with corticosteroids diminishes the rate.

In the light of these studies of collagen types we can make some critical appraisal of their importance in fibrotic lung disease. The changes reported have in general been quite small and the overlap between patients and control subjects means that measurements in individual patients are of little value. Furthermore, the shifts to excessive type I collagen are quite a late event and unlikely to constitute an important step in the pathology of the disease. The possibility, however, of obtaining serial measurements of type III procollagen peptides (or other indices of collagen metabolism) in the same patients and using these with

other data in the assessment of prognosis and response to treatment is more encouraging and should be pursued.

Pathways leading to changes in collagen metabolism in pulmonary fibrosis

The deposition of collagen is a relatively late event in the sequence of steps broadly described as the "repair cascade," a process central to normal body homeostasis. To see it in isolation is misleading and likely to produce a distorted vision of the pathogenesis of fibrosing lung disorders. What is important here is that in normal scar formation the collagen deposition is limited and apparently reversible, whereas in various pathological states, including some forms of pulmonary fibrosis, it seems to be progressive and does not appear to be reversible.

The early pathways leading to lung damage and eventual collagen deposition are now beginning to be understood, although the pathways are likely to be different for different forms of pulmonary fibrosis. For example, in asbestosis and pneumoconiosis the nature of the causative agents is known in some detail and the early pathways may be very different from those where pulmonary fibrosis occurs as a side effect of bleomycin treatment or in cryptogenic fibrosing alveolitis. In the case of dust induced diseases interaction with alveolar cells may be the primary event, whereas for bleomycin there is evidence that interaction of bleomycin with DNA (in the presence of iron and oxygen), to form an active oxygen species, is probably the important primary event (see ref 38 for review). In cryptogenic fibrosing alveolitis (or idiopathic pulmonary fibrosis) in man the initial cause is unknown but the presence of immune complexes deposited on endothelial surfaces may be an important initiating step.³⁹ Whatever the initial cause, an influx of inflammatory cells into the lung is common to all these disorders. The nature of these cells may in part depend on the initiating agent but large numbers of neutrophils, macrophages, and lymphocytes are often seen. The persistent presence of these cells and other plasma elements (that is, platelets, fibronectin, plasma derived growth factors) is almost certainly important not only in the injury itself but also for the repair mechanism (fig 3).

There is now strong evidence that cells of the immune and reticuloendothelial system may play a part in the regulation of collagen metabolism in fibrotic lung disorders (see refs 40 and 41 for review). Interest in these cells in pulmonary fibrosis was initially prompted by studies suggesting that peritoneal macrophages exposed to mineral fibres release a factor that stimulates collagen production by fibroblasts.⁴² More recent studies of alveolar macrophages derived from man and experimental animals have tended to

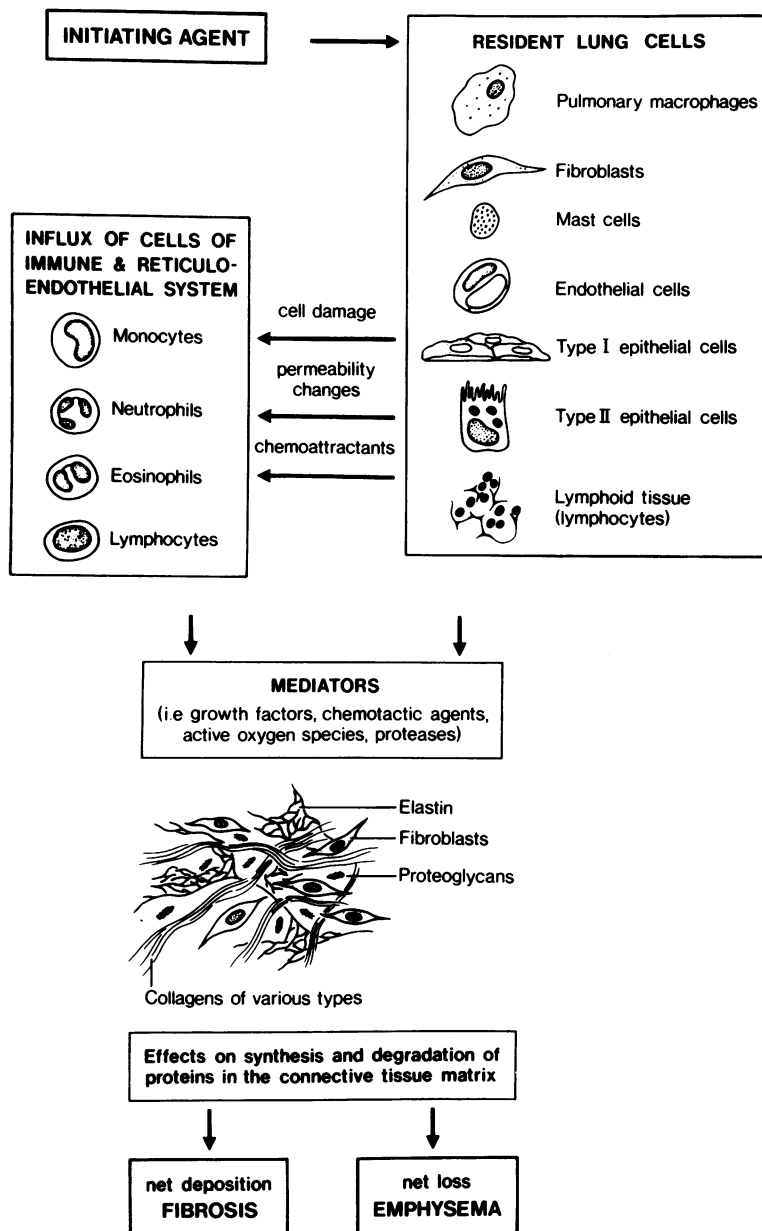


Fig 3 Possible cellular interactions leading to changes in synthesis and degradation of connective tissue proteins.

support this view, indicating that the macrophage is capable of releasing growth factors that lead to fibroblast replication.⁴³⁻⁴⁵ Here an important observation is that alveolar macrophages from patients with idiopathic pulmonary fibrosis tend to secrete a growth factor spontaneously.⁴⁶ The alveolar macrophage may have a role for other reasons. This cell is

capable of releasing a neutrophil chemotactic factor⁴⁷ and fibronectin, which is a chemoattractant for fibroblasts.⁴⁸ It can also produce active oxygen species that are capable of degrading a wide range of macromolecules, leading to eventual cell death. Thus mechanisms exist whereby the alveolar macrophage, by releasing various mediators, is capable not only of

expanding the fibroblast population and attracting fibroblasts to the site of the injury but also of attracting inflammatory cells and thereby causing further cell damage.

Another possibility is that cells, cell fragments, or mediator are derived from the circulation. It has been recognised for many years that in the earliest events leading to pulmonary fibrosis there is an exudative phase with appreciable accumulation of fluid derived from the blood. It has also been suggested that exudation follows from capillary endothelial damage and that this may underlie the primary events in the pathways leading to pulmonary fibrosis.⁴⁹ Considerable protein exudation has been demonstrated during bleomycin induced pulmonary fibrosis by measurement of radioisotopically labelled albumin in the pulmonary extravascular space.⁵⁰ The influx of various agents from the circulation could have appreciable effects on collagen metabolism in the lung, overwhelming any effects associated with resident cells (that is, alveolar macrophages). This could be due to agents free in plasma or those derived indirectly from cells or platelets that enter the lung. Platelets contain an extremely potent mitogen for fibroblasts (platelet derived growth factor), which is also a chemoattractant for fibroblasts.⁵¹

Lymphocytes and neutrophils are both present in increased numbers, particularly in the early stages of pulmonary fibrosis. Lymphocytes are known to release a host of factors capable of stimulating increased collagen secretion by fibroblasts, causing fibroblast proliferation and migration (see ref 52 for review). Furthermore, studies of bleomycin induced fibrosis in T cell depleted mice and thymectomised rats suggested that these animals develop a less intense lesion,^{53 54} which gives *in vivo* credence to their role. Such evidence has not yet been obtained for macrophages.

There is also a large influx of neutrophils in pulmonary fibrosis, probably stimulated by release of various chemoattractants. Fibronectin has already been mentioned and products of cellular damage may also be important. Breakdown products of collagen are known to be chemoattractants for neutrophils^{55 56} as well as fibroblasts.⁵⁷ In this way a cascade effect develops, bringing more neutrophils to the site of injury and leading to further damage as well as repair by fibrosis. This may explain the progressive nature of the damage in many of the fibrotic lung disorders. Clearly there are many mediators, derived from various sources, that are capable of inducing changes in collagen metabolism consistent with the responses occurring during pulmonary fibrosis. This information comes from *in vitro* studies, however; there is so far little *in vivo* evidence that they have a role. Determining which, if any, of these factors is

important in the pathways leading to pulmonary fibrosis constitutes a major challenge for the future.

Pulmonary emphysema: is collagen important?

Advances in emphysema research have on the face of it outstripped those in fibrosis. Some workers now believe that the pathways underlying the development of emphysema are sufficiently well understood to permit evaluation of treatment directed at the proposed molecular defect. Excessive elastin breakdown is thought to be crucial. Antielastase treatment has been proposed and the use of α_1 antitrypsin replacement therapy is currently being evaluated in clinical trials. Its rationale is not the subject of this editorial, and this approach and the pathways of elastin metabolism in relation to emphysema are described elsewhere.^{58 59} Rather, the aim here is to examine critically the hypothesis that emphysema is a disorder exclusively of elastin metabolism.

Pulmonary emphysema and fibrosis has traditionally been thought of as opposites. Emphysema is characterised histologically by enlarged air spaces and physiologically by increased compliance and diminished recoil. This contrasts with pulmonary fibrosis, where there is a decreased compliance and a reduction in lung volume. They have also by and large been thought of as diseases of elastin and collagen respectively. The reasons for this are not clear and should be reappraised. In biochemical studies where elastin and collagen have been examined the changes in elastin have been similar to those in collagen.^{15 60 61} Studies on emphysema are controversial, with evidence for no change in elastin, expressed either as total lung content^{62 63} or as a concentration,⁶²⁻⁶⁴ although a more recent study suggested a decreased concentration as a proportion of connective tissue components.⁶⁵

Differences also exist in the way researchers in the two areas have directed their efforts. In pulmonary fibrosis they have concentrated almost exclusively on the synthetic pathways, whereas in emphysema effort has been directed toward degradation. This polarisation has not been entirely useful and it may have been more productive to examine the balance between synthesis and degradation of connective tissue components in these disorders, since both may be important (fig 2).

The current concept of emphysema is that it is a disease which depends on changes in elastin degradation, a view based on two observations. Firstly, instillation of pancreatic elastase into lungs of experimental animals induced a lesion typical of emphysema. Later neutrophil elastase was shown to produce a similar response. The role of collagen was thought to be unimportant because instillation of bacterial collagenase did not produce such a response

(see ref 66 for review). The second observation was the discovery of the genetic disorder of α_1 antitrypsin deficiency, in which individuals were found to be susceptible to early onset of emphysema.⁶⁷ This led to the so called protease-antiprotease theory of emphysema, in which elastolytic enzymes were normally met and controlled by a screen of α_1 antitrypsin. Elastin degradation and emphysema occurred when the enzyme load exceeded the inhibitory screen.

These observations alone fall short of proving that only elastin has a role. The lack of effect by collagenase depends on the nature of the enzyme used. There are now known to be various collagenases, which have different specificities for the different collagen types (see previous section on collagen structure and metabolism). Here it is important that neutrophil elastase is capable of degrading types III and IV collagens as well as elastin.⁶⁸⁻⁶⁹ The results of studies of metabolism in experimental animals are somewhat equivocal. They indicate that there is increased turnover (that is, synthesis and degradation) of collagen and proteoglycans as well as elastin. Furthermore, at a time when concentrations of collagen and elastin are normal there is still histological evidence of emphysema.⁷⁰ This is consistent with the results of some studies in man, in which total lung elastin contents were not observed to alter in patients with emphysema.^{59,60}

Further, even if elastin breakdown does constitute an initial step in the pathways leading to emphysema elastin breakdown products, or damage caused by elastase, are known to lead to an inflammatory cell influx. These, as discussed above, are capable of releasing enzymes or oxygen radicals that can lead to subsequent collagen breakdown. Perhaps therefore the view of emphysema as just an elastin disease dependent on elastase-antielastase balance is premature. Figures 2 and 3 describe more fully some of the potential pathways, and may be useful in designing experiments to elucidate the mechanism of this disease.

GJ LAURENT

Lung Biochemistry Unit

Department of Thoracic Medicine

Cardiothoracic Institute

London SW3 6HP

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