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Role of Mesothelial and Submesothelial Stromal Cells in Matrix Remodeling Following Pleural Injury

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The pleural response to injury is a complex and poorly understood multifactorial process that can result in the development of fibrosis or obliteration of the pleural space. Pleural fibroblasts are considered the main source of extracellular matrix but cell culture studies have demonstrated synthesis of matrix components by mesothelial cells. We assessed the mesothelial cell contribution to extracellular matrix during pleural healing using immunohistochemical technique. Paraffin-embedded tissue of 3 normal adult lungs and 7 adults with active pleuritis were studied using monoclonal antibodies to cytokeratin, type IV collagen, vimentin, and type I procollagen (PCI). Normal pleuras had a single layer of cytokeratin-positive and PCI-negative mesothelium over a thin, continuous type IV collagen-positive basement membrane and PCI-negative submesothelial stroma. Areas of active pleuritis showed loss of the continuous linear staining with anti-type IV collagen antibody. Co-expression of cytokeratin, vimentin and PCI was identified in spindle and/or cuboidal cells located in the fibrin layer, submesothelial connective tissue layer, or on the pleural surface. These findings suggest that reactive mesothelial cells play an active role in the production of extracellular matrix during pleural injury, and that disruption of the submesothelial basement membrane is a key event in determining subsequent fibrous organization of pleural exudate. (Am J Pathol 1993, 142:547–555)

Injury to the pleura is a common phenomenon that can be caused by numerous etiologic agents. However, surprisingly little is known about the cellular mechanisms of the human pleural response to injury or of the factors that determine its clinical outcome. The most common consequence of pleural injury is the development of an exudative effusion, which in most instances resolves without significant architectural changes. However, in some cases, pleural injury leads to submesothelial pleural fibrosis, the formation of fibrovascular adhesions, or even to fibrous obliteration of the pleural space.

The structural integrity of the basement membrane (BM) is critical in determining the pattern of tissue repair following many forms of severe organ injury.[1] Preservation of the BM allows orderly repair with the proliferation and migration of viable parenchymal cells from the margins of tissue injury with repopulation of the pre-existing connective tissue scaffolding. Destruction of this scaffolding precludes restoration of normal architecture and is often associated with the development of a fibroproliferative reaction, with resultant scarring and loss of normal tissue function.

Animal studies have demonstrated that acute injury to serosal or pleural surfaces leads to mesothelial denudation, fibrin deposition on the denuded serosal surfaces, and edema of the underlying connective tissue.[2,3] When the injury is sufficiently localized, mesothelial cells at the edges of the injured and denuded area proliferate and eventually repopulate the denuded surface.[3] By contrast, pleural injuries associated with more extensive denudation, exudation, and inflammation often show pleural fibrosis and adhesion formation.[2]

A variety of cellular components are believed to participate in the pleural response to injury, including mesothelial cells, submesothelial connective tissue cells, and resident and migratory inflammatory cells. Submesothelial fibroblast-like cells are believed to be the major source of the type I collagen-rich collagenous matrix that accumulates at sites of pleural fibrosis. However, *in vitro* studies indicate that mesothelial cells, which may retain many of the cyto-

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logic features of native mesothelial cells, also have the capacity to produce a variety of matrix macromolecules, including interstitial collagens, fibronectin, and basement membrane components.[4–6]

To better understand the mechanisms of matrix remodeling in pleural injury, and the possible contribution(s) of mesothelial cells, we examined sections of pleura from patients with organizing pleuritis and performed correlative immunohistochemical studies using monoclonal antibodies to selected matrix macromolecules. In particular, we used a monoclonal antibody specific for the amino-terminal precursor domain of human type I procollagen to identify and localize activated connective tissue synthesizing cells and areas of recently deposited collagenous matrix.[7,8] We also used a monoclonal antibody specific for the "7S" amino-terminal cross-linking domain of human type IV collagen to assess the distribution and integrity of submesothelial basement membranes.[7]

Materials and Methods

Pulmonary specimens were obtained from the files of the Department of Pathology at The Jewish Hospital of St. Louis. Seven specimens were open biopsies of patients with active pleuritis or fibrous pleural adhesions. Three normal adult lungs were retrieved from the autopsy files. Pertinent demographic data are summarized in Table 1. All the tissues had been fixed in 10% neutral buffered formalin and embedded in paraffin. Hematoxylin-eosin–stained sections were available for histologic examination.

Immunoperoxidase studies were performed using monoclonal rat anti-type I procollagen antibody (PCI) (50 μg/ml, purified IgG from hybridoma M57) and mouse anti-human type IV collagen antibody (CIV)(1:800, mouse ascites). The mouse and rat monoclonal antibodies were prepared and characterized by Dr. John McDonald and coworkers, and used as previously described.[7] Parallel sections were also immunostained with mouse anti-cytokeratin (AE1/AE3; Biogenex, San Ramon, CA, prediluted), and mouse anti-vimentin (Biogenex, San Ramon, CA, prediluted) antibodies. All sections, except those incubated with anti-vimentin antibody, were pretreated with 1% (w/v) trypsin (Sigma Chemical Co, St. Louis, MO) for 20 minutes at room temperature to "unmask" antigenic determinants. Nonspecific immunoglobulin binding sites were blocked with goat serum, and sections were incubated with primary antibody for 2 hours at 37 C. Negative controls included parallel sections incubated with normal immunoglobulin or serum. Antibody binding sites were visualized using an indirect biotinylated goat anti-mouse (or goat anti-rat) secondary antibody/streptavidin-horseradish peroxidase detection system with diaminobenzidine as substrate.

Results

Histology

The histologic features of the pleura for each case are summarized in Table 1. Areas identified as *normal pleura* showed a single layer of flattened mesothelial cells overlying a thin fibrous layer that contained only small numbers of spindle cells. These layers were in turn supported by a relatively dense elastic layer, a looser fibrovascular layer of variable thickness, and an internal elastic fiber layer that merged imperceptably with the elastic fibers of the subjacent alveolar walls. The vascular layer was traversed by elastic fibers oriented perpendicular to the pleural surface and contained scattered spindle cells and rare lymphocytes, monocytes, and mast cells.

Areas of *acute pleuritis* (case 4) were characterized by extensive mesothelial denudation, fibrin deposition on the pleural and residual mesothelial surfaces, and the presence of edema and inflammatory

Table 1. *Clinical Data and Histologic Diagnoses of Cases with Pleuritis and Normal Pleura*

	Case	Age (yr)	Diagnoses
Normal	1	72	Cardiac arrythmia; sepsis
	2	61	Myocardial infarction
	3	82	Atherosclerosis; pulmonary emboli
Acute pleuritis	4	60	Bronchiectasis; bronchiolitis obliterans; organizing pneumonia; acute bronchopneumonia
Organizing pleuritis	5	37	Systemic lupus erythematosus; acute bronchopneumonia
	6	61	Carcinoma
	7	76	Empyema
	8	54	Nonspecific interstitial fibrosis; calcified granulomata; intralveolar hemorrhage; emphysema
	9	46	Carcinoma
	10	59	History of oat cell carcinoma and pneumothorax

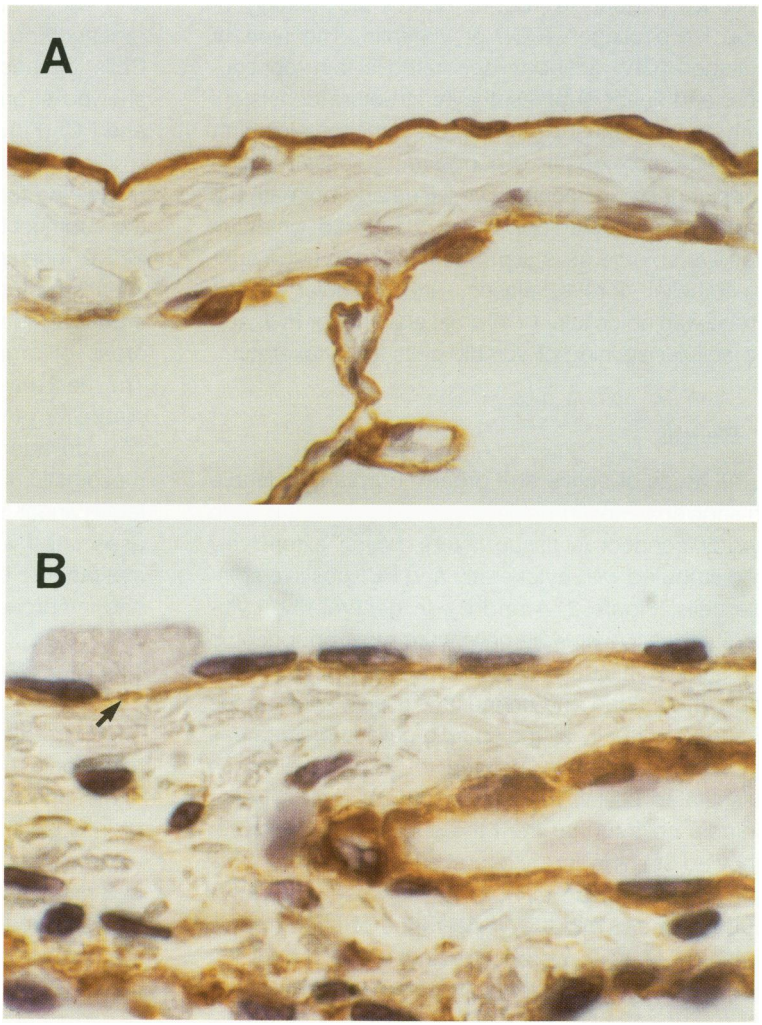

Figure 1. *Normal pleura.* **A:** *Mesothelial and alveolar epithelial cells show strong immunostaining for cytokeratin. The pleural space is at top (original magnification ×525).* **B:** *The submesothelial basement membrane (arrow) reacts with antibodies to type IV collagen. The alveolar and vascular basement membranes are also reactive (original magnification ×1000).*

cells in the submesothelial connective tissue. Most of the inflammatory cells were neutrophils but scattered monocyte/macrophages and lymphocytes were also present. The surface fibrin layer was hypocellular, containing only rare spindle and inflammatory cells. Mesothelial cells adjacent to denuded areas showed cellular and nuclear enlargement.

Areas of *organizing pleuritis* (cases 5 to 10) showed thickening of the pleura with abundant spindle cells and inflammatory cells in the submesothelial connective tissue layer. Most of the inflammatory cells were lymphocytes and plasma cells but scattered neutrophils or eosinophils were also present. Four of the six cases of organizing pleuritis showed no significant amounts of fibrin (cases 6, 7, 9, and 10); however, two specimens (cases 5 and 8) showed a surface fibrin layer containing scattered fibroblast-like cells, as well as cuboidal cells that resembled hypertrophic mesothelial cells. Hypertrophic mesothelial cells were sometimes identified overlying adjoining areas of mildly inflamed but architecturally normal pleura (case 6). Four specimens (cases 6, 8, 9, and 10) also demonstrated cellular adhesions and areas of intrapleural organization. These areas were characterized by accumulations of basophilic matrix surfaced by cuboidal mesothelial cells, and containing hypertrophic spindle cells, small blood vessels, and variably prominent infiltrates of mononuclear inflammatory cells and eosinophils. Case 10 showed the most "mature adhesions" with relatively complete mesothelial surfaces overlying a well-vascularized, more densely fibrous stroma containing small numbers of lymphocytes and monocytes.

Immunohistochemistry

Normal Pleura

The mesothelial layer of normal pleura showed strong and uniform staining with the anti-cytokeratin

antibody (Figure 1A), but no detectable staining for type I procollagen (PCI) or vimentin. The type IV collagen (CIV) antibody decorated a thin, continuous, and linear submesothelial structure consistent with the basal lamina (Figure 1B). Immunostaining for CIV was also identified surrounding vessels in the subjacent pleural connective tissue and beneath the underlying alveolar epithelium. Scattered vimentin-positive spindle cells were identified within the submesothelial fibrous, elastic, and vascular layers. There was no cellular or stromal staining for PCI, and no cellular staining of spindle cells for cytokeratin.

Pleuritis

All areas of active and organizing pleuritis (Table 2) showed vimentin-positive spindle cells in the fibrin and/or connective tissue layers, which extensively codistributed with cytokeratin and PCI-positive spindle cells (Figure 2, A and B). In general, the cytokeratin-positive spindle cells were most abundant in the superficial submesothelial regions or at the interface of the fibrin and connective tissue layer (cases 5 and 8). Virtually all the spindle cells in these areas showed cytoplasmic staining for PCI, usually with associated staining of the pericellular matrix. Some spindle cells further from the surface or fibrin layer showed staining for cytokeratins without detectable cellular expression of PCI. In four cases, round or cuboidal cells with the appearance of hypertrophic mesothelial cells were seen within the organizing fibrinous exudate; these cells coexpressed cytokeratins and vimentin, and in three specimens (cases 5, 7, and 8) reacted with antibodies PCI (Figure 3, A and B). In cases 6, 8, and 10, areas of intact or regenerating mesothelial lining were also identified. Cells in these areas appeared hypertrophic and showed strong cytoplasmic staining for cytokeratin and PCI (Figure 4, A and B).

In all the cases of pleuritis there was extensive loss of staining for type IV collagen with apparent loss of the submesothelial basement membrane in areas of active inflammation. Specifically, the characteristic linear structure was either absent or discontinuous in areas of mesothelial denudation and underlying areas of organizing intrapleural fibrinous exudate. The most mature adhesions, and some areas of intrapleural organization, showed linear staining for type IV collagen beneath regenerative surface mesothelium. Discontinuous layers of type IV collagen linear staining (Figure 5) were identified and associated with spindle cells in the superficial submesothelial connective tissue of thickened pleura and in fibrous adhesions of cases 6 and 10.

Discussion

The visceral and parietal pleura are derived from the embryonic mesoderm and are lined by a single layer of mesodermally derived epithelioid cells, which rest on a basement membrane.[9] In the visceral pleura, the mesothelial basement membrane is supported and mechanically linked to the underlying lung by a complex connective tissue composed of at least four morphologically distinct compartments. These include a thin, loose submesothelial fibrous layer, a dense external fibroelastic layer, a looser vascularized layer, and an internal elastic layer. The mesothe-

Table 2. *Immunohistochemistry of Cases with Pleuritis*

	Case		Keratin	Vimentin	Type I procollagen
Acute pleuritis	4	Fibrin layer	C+	S+	C+
		Connective tissue layer	S+	S+	S+
Organizing pleuritis	5	Fibrin layer	S and C +++	S and C +	S and C +++
		Connective tissue layer	S+++	S and C ++	S+++
	6	Fibrin layer			
		Connective tissue layer	S+	S++	S++
	7	Fibrin layer			
		Connective tissue layer	S and C +++	S and C +++	S and C +++
	8	Fibrin layer	S and C +	S+	S++
		Connective tissue layer	S and C ++	S++	S and C ++
	9	Fibrin layer			
		Connective tissue layer	S+	S+	S+++
	10	Fibrin layer			
		Connective tissue layer	S++	S+	S++

Immunohistochemical staining pattern of cuboidal (C) and spindle (S) cells using anti-cytokeratin, anti-vimentin, and anti-type I procollagen antibodies. No cuboidal cells were identified in the connective tissue layer of cases 4, 6, 9, and 10.

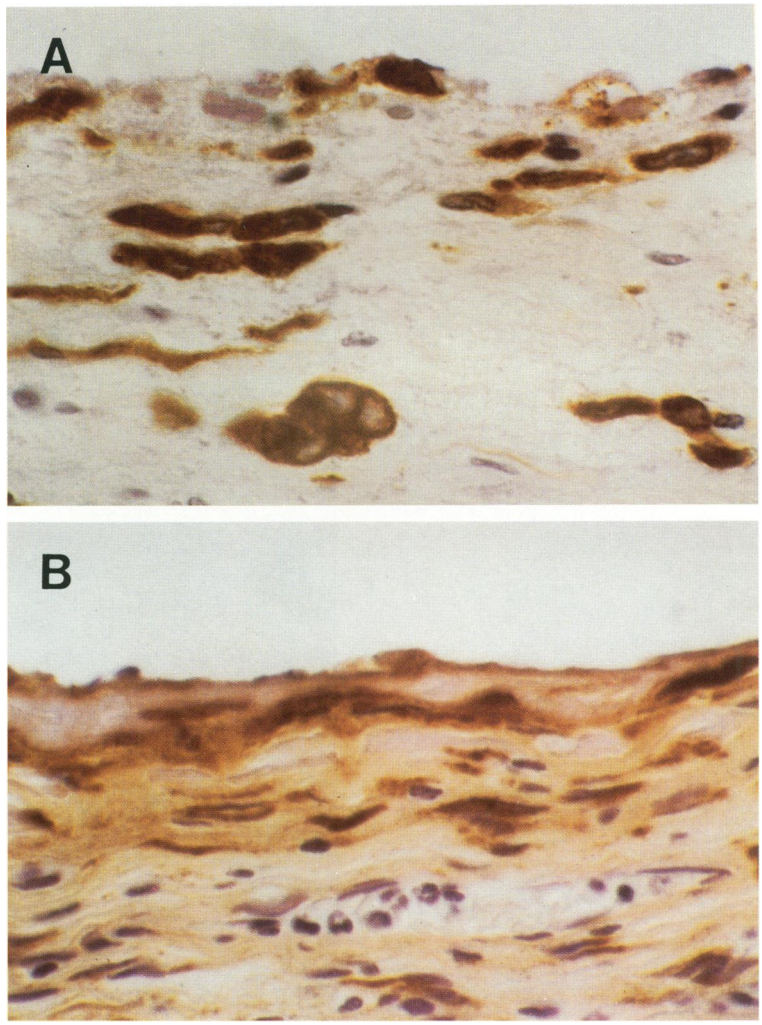

Figure 2. *Organizing pleuritis.* A: *Submesothelial spindle cells are cytokeratin positive (original magnification ×1000).* B: *Submesothelial spindle cells show strong cytoplasmic staining with anti-type I procollagen. Weaker staining of the surrounding extracellular matrix is also present (original magnification ×1000).*

lial cell layer serves as a barrier between the pleural cavity and the underlying connective tissue and is thought to have roles in the elaboration and turnover of pleural fluid. In particular, these cells secrete hyaluronic acid and phosphatidylcholine, molecules that may participate in the transmission of mechanical forces between the lung and chest wall.[10] Mesothelial cells are also believed to contribute to the formation of the underlying mesothelial BM.

Numerous injurious agents are known to damage the pleura, eliciting changes that range from the development of transient effusion to adhesions and fibrosis. Morphologic assessment of the progression of pleural response to injury has been performed in a few animal models. For example, Wheeldon et al[3] instilled nitric acid intrapleurally in sheep and found that after 30 minutes the mesothelium was desquamated and the basement membrane and connective tissue were exposed. A fibrin layer was formed within 24 hours and interstitial edema was prominent in the underlying connective tissue. Mesothelial regeneration at the edges of the injured area was evident by the fourth day. These mesothelial cells recolonized the denuded area in a centripetal manner, resulting in restoration of the normal architecture. Strange et al[2] performed a similar study in rabbits. They examined three different animal models using intrapleural instillation of tetracycline, carrageenan, or bacteria. The tetracycline and empyema models showed extensive mesothelial denudation, marked pleural thickening with connective tissue proliferation, angiogenesis, and formation of fibrous adhesions. By contrast, carrageenan administration elicited a less intense pleural reaction with minimal mesothelial desquamation, and only mild focal pleural thickening that evolved with complete restoration of the normal pleural architecture. These observations suggest that the integrity of the mesothelium (and/or submesothelial matrix) play critical roles in determining the course of pleural healing.

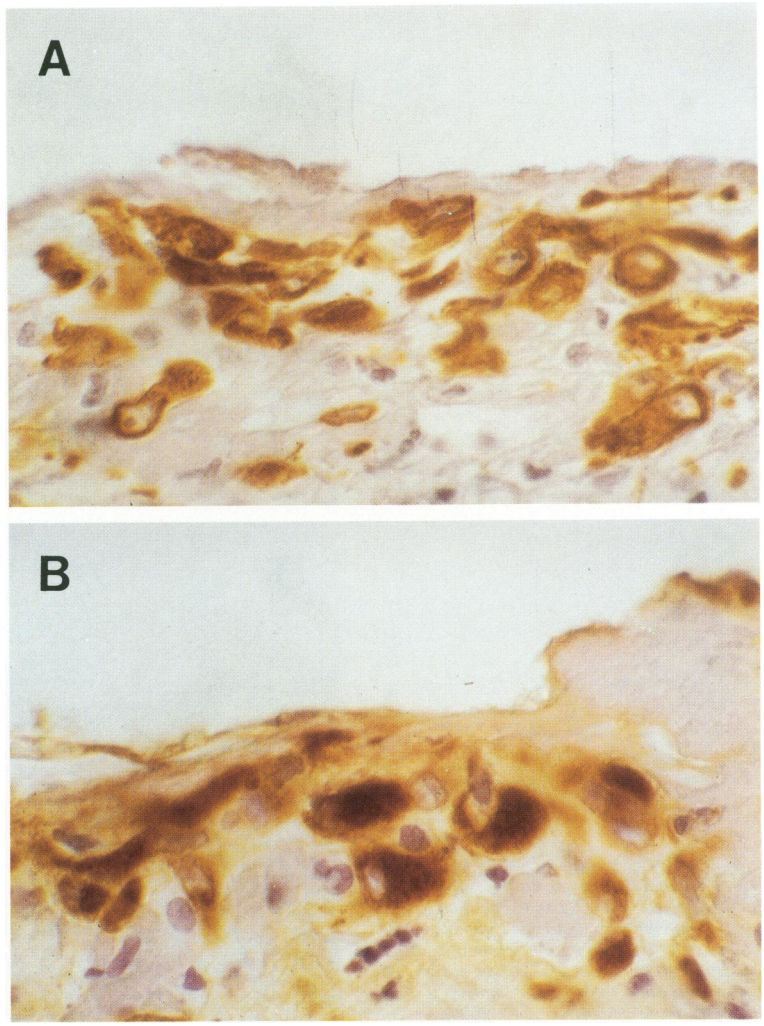

Figure 3. *Organizing pleuritis. Cytokeratin* (A) *and PCI* (B) *cytoplasmic staining of cuboidal cells located in the fibrin layer (original magnification ×1000).*

The majority of studies of mesothelial injury and repair have been performed in peritoneal injury models.[11,12] As result of these studies, several nonmutually exclusive hypotheses have been advanced regarding the origin of the regenerating mesothelium. Whitaker and Papadimitriou[13] favored the concepts of centripetal healing of injured mesothelium and implantation of mesothelial cells from apposing serosal surfaces. Less well supported is the hypothesis that viable mesothelial cells, released into the pleural fluid, attach to denuded areas and proliferate to restore a continuous mesothelial layer.[14] Other investigators have suggested that multipotential subserosal cells serve as progenitors for the regenerating mesothelial cells.[15,16] Subserosal cells in areas of active serositis coexpress cytokeratins and vimentin,[15,16] resembling the cytokeratin-, vimentin-, and PCI-positive spindle cells identified in areas organizing pleuritis. Our study does not allow us to determine the relationship between the submesothelial spindle shaped cells and the regenerating mesothelial cells. However, we favor the hypothesis advocated by Bolen et al,[15] that multipotential subserosal cells are capable of replication and differentiation to surface mesothelium.

Cell cultures studies have demonstrated the production of matrix components by isolated mesothelial cells. Harvey and Amlot[4] found that the predominant collagens produced by human mesothelial cells were type I and III, and similar results were reported by Stylianou et al.[6] Rennard and coworkers[5] used metabolic labeling and immunoprecipitation techniques to confirm the production of type I and III collagen by cultured rat mesothelial cells, but also demonstrated the production of other matrix components including type IV collagen, tropoelastin, laminin, and fibronectin. Furthermore, ultrastructural studies of the cultures demonstrated the accumulation of a subcellular matrix that appeared to recapit-

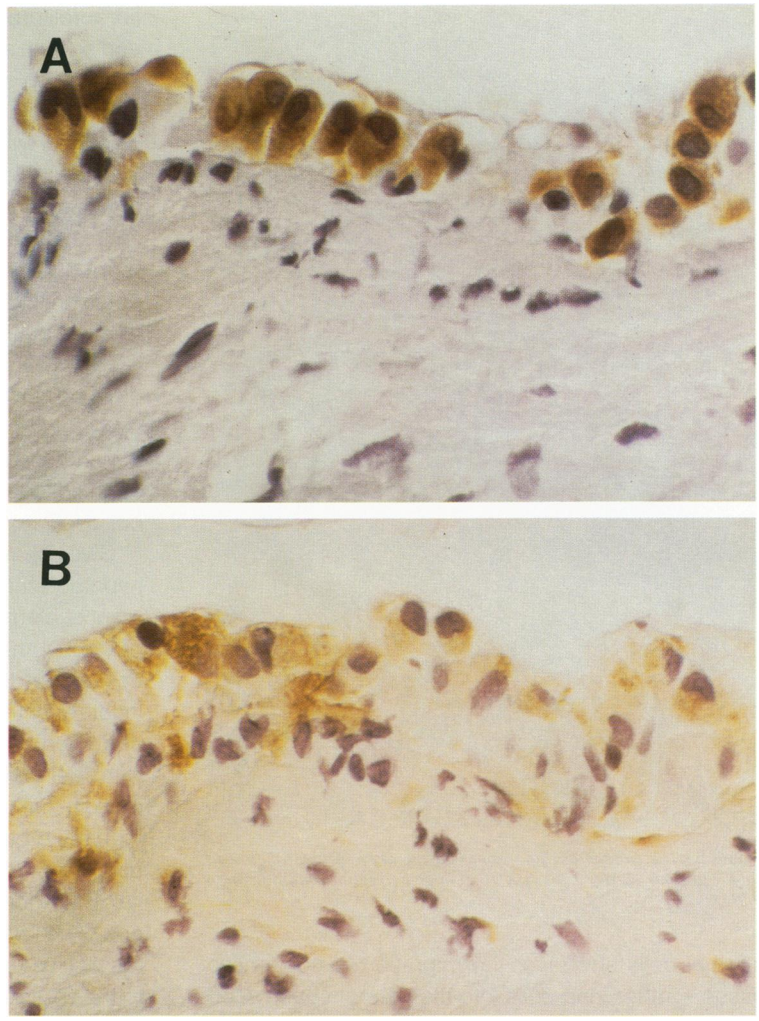

Figure 4. *Coexpression of cytokeratin* **(A)** *and procollagen type I* **(B)** *by reactive mesothelial cells (original magnification × 1000).*

ulate normal pleural architecture, ie, with polarized mesothelial cells resting on an electron-dense basal lamina-like structure supported by a matrix containing interstitial collagen fibers. These findings are consistent with our observations and the suggestion that these cells contribute to type I collagen accumulation, at least in the setting of severe pleural injury. The absence of detectable cytoplasmic staining for type IV collagen could reflect differences in relative sensitivity of the immunohistochemical and immunoradiochemical assay, or the antigenic specificity of the type IV monoclonal, which preferentially recognizes an epitope associated with the cross-linked amino-terminal domain of type IV collagen.

Immunohistochemical studies on normal adult pleura using the anti-type IV collagen monoclonal antibody showed a thin and continuous submesothelial BM zone underlying all areas of cytokeratin-positive mesothelium. Staining was interrupted or lost in all areas of acute or organizing pleuritis, particularly where the overlying mesothelial layer was absent. Similar results were reported by Brockmann et al,[16] who failed to detect immunostaining for type IV in areas of pleural injury and early mesothelial regeneration. Although immunohistochemical techniques cannot distinguish between loss of the BM and alterations in the accessibility of antigenic determinants, the former possibility is consistent with the ultrastructural findings of Wheeldon et al[3] who observed absence of the basal lamina in areas of injured pleura, including areas recolonized by mesothelial cells. The ability of regenerating mesothelial cells to synthesize BM components is consistent with the occurrence of linear type IV staining beneath hypertrophic mesothelial cells overlying areas of pleural space organization and adhesion formation, and in some associated areas of submesothelial stroma.

A variety of factors could contribute to the activation and proliferation of mesothelial and subserosal

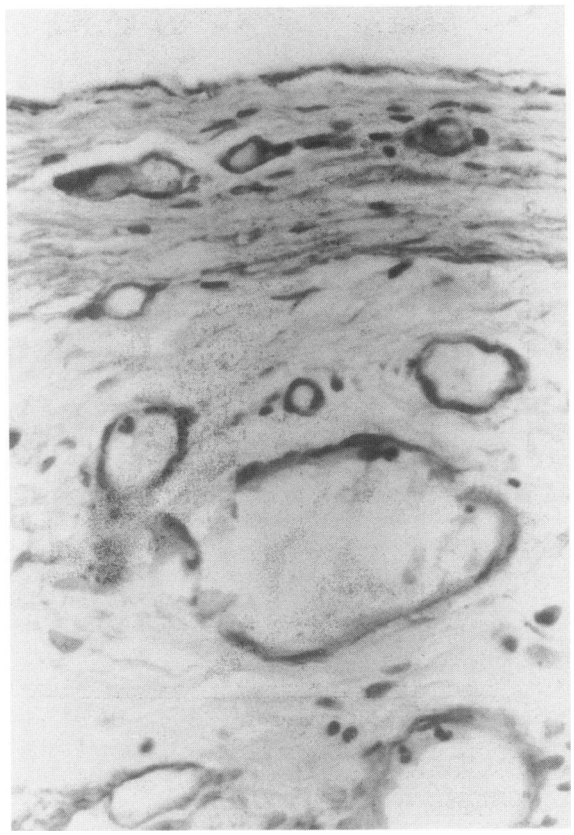

Figure 5. *The submesothelial stroma in an area of pleural fibrosis shows fibrillar staining for type IV collagen (original magnification ×1000).*

stromal cells and favor the migration of connective tissue synthesizing cells into the pleural space. Certain cytokines, fibrinopeptides, matrix proteins, and matrix protein-derived peptides are chemotactic for fibroblasts.[17] In this regard, recent studies by Kuwhara et al[18] have shown that rat mesothelial cell-derived fibronectin is chemotactic for rat lung fibroblasts *in vitro*. Because macrophages are prominent in areas of organizing pleuritis,[2] we speculate that macrophage-derived cytokines, such as transforming growth factor-β, platelet-derived growth factor, and tumor necrosis factor, are elaborated at sites of pleural injury and play key roles in modulating pleural fibroproliferative reactions. For example, transforming growth factor-β can up-regulate type I procollagen gene expression and production by fibroblasts and can also influence the expression of matrix protein receptors, and modulate the production of matrix degrading enzymes and inhibitors. Similar effects could be exerted on mesothelial and submesothelial stromal cells.

There is considerable interest in the possible role(s) of fibrin or products of the coagulation and fibrinolytic pathways in influencing inflammatory and fibroproliferative reactions.[19,20] The accumulation and organization of fibrinous exudate is conspicuous at sites of pleural injury.[2,3] Furthermore, thrombin can elicit the migration and proliferation of rat mesothelial cells[21] as well as fibroblasts.[22] Persistence of a fibrin layer has even been correlated with the development of pleural fibrosis[23]; however, it is difficult to differentiate between the direct effects of fibrin or related products and the extent and severity of initiating and perpetuating injuries. In any case, the cellular regulation of matrix production at sites of pleural injury is likely to be complex. For example, *in vitro* studies have demonstrated thrombin-induced production of prostaglandin E_2 by isolated mesothelial cells[24]; and prostaglandin E_2 is known to suppress proliferation and collagen production by lung fibroblasts in culture.[25]

Given these data and previous observations, we hypothesize that severe injuries favor the development of pleural fibrosis by compromising the integrity of the submesothelial basement membrane (Figure 6). Loss of the BM in turn influences the anatomic localization of the ensuing fibroproliferative and angiogenic reactions. As Strange et al[2] suggested with their animal studies, agents that do not elicit mesothelial denudation are not likely to produce pleural fibrosis. Because areas of mesothelial denudation also show associated loss of the submesothelial BM, destruction of the submesothelial matrix could be critical in allowing matrix-producing cells (as well as capillary endothelial cells) to gain access to the pleural space and organize areas of intrapleural exudate. Adhesions or fibrous obliteration of the pleural space could result as a consequence of severe injury involving both the visceral and parietal pleura, or apposed visceral pleural surfaces. Thus, the severity and extent of the initiating and perpetuating injuries may be critical in determining the pattern of the subsequent pleural fibroproliferative reaction, thereby determining the ultimate outcome of pleural injury.

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