Systemic sclerosis and idiopathic interstitial pneumonia:
histomorphometric differences in lung biopsies*, **

Esclerose sistêmica e pneumonia intersticial idiopática:
diferenças histomorfométricas em biópsias pulmonares

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Abstract

Objective: The aim of this study was to examine the parenchymal and extracellular matrix remodeling process in two histologic patterns—nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP)—in cases of idiopathic and sclerosis/systemic sclerosis (SSc)-associated interstitial pneumonia. Methods: We examined 15 cases of idiopathic NSIP, 10 cases of idiopathic UIP, 5 cases of SSc-UIP and 9 cases of SSc-NSIP. In the lung parenchyma, epithelial cells, endothelial cells and myofibroblasts were evaluated by immunohistochemical staining, whereas histochemical staining was used in order to evaluate collagen/elastic fibers in the extracellular matrix.

Results: The percentage of surfactant protein A-positive epithelial cells was significantly greater in idiopathic NSIP than in SSc-NSIP, as well as being greater in idiopathic UIP than in SSc-UIP. Idiopathic NSIP and idiopathic UIP presented significantly higher immunoeexpression of alpha smooth muscle actin in myofibroblasts than did SSc-NSIP and SSc-UIP. The percentage of CD34 endothelial cells in the pulmonary microvasculature was significant lower in idiopathic UIP than in SSc-UIP. The density of collagen fibers was significantly greater in idiopathic NSIP and idiopathic UIP than in SSc-NSIP and UIP. In contrast, the elastic fiber density was significantly lower in idiopathic UIP than in SSc-UIP.

Conclusions: Increased collagen synthesis, destruction of elastic fibers, high myofibroblast proliferation and poor microvascularization might represent a remodeling process found in idiopathic interstitial pneumonia, whereas the reverse might represent a repair process in SSc-associated interstitial pneumonia.

Keywords: Epithelial cells; Neovascularization, pathologic; Collagen; Elastin; Idiopathic interstitial pneumonias; Scleroderma, systemic.

Resumo

Objetivo: O objetivo deste trabalho foi examinar o processo de remodelamento no parênquima e na matriz extracelular em dois padrões histológicos—pneumonia intersticial não-específica (PINE) e pneumonia intersticial usual (PIU)—em casos associados à esclerose idiopática/esclerose sistêmica (ES). Métodos: Investigamos 15 casos de PINE idiopática, 10 casos de PIU idiopática, 5 casos de PIU associada à ES (PIU-ES) e 9 de PINE associada à ES (PINE-ES). No parênquima pulmonar, as células epiteliais, células endoteliais e miofibroblastos foram avaliados através de coloração imuno-histoquímica, ao passo que a coloração histoquímica foi utilizada para avaliar as fibras elásticas e de colágeno na matriz extracelular.

Resultados: A porcentagem de células epiteliais positivas para proteína A do surfactante foi significativamente maior nos casos de PINE idiopática do que nos de PINE-ES, assim como nos casos de PIU idiopática do que nos de PIU-ES. A PINE e a PIU idiopáticas apresentaram valores significativamente maiores de immunoeexpressão de alfa actina de músculo liso nos miofibroblastos do que a PINE-ES e a PIU-ES. A porcentagem de células endoteliais CD34 na microvasculatura pulmonar foi significativamente menor na PINE idiopática do que na PIU-ES. A densidade de fibras do colágeno foi significativamente maior em ambas as formas idiopáticas de PINE e PIU do que na PINE-ES e PIU-ES. Em contraste, a densidade de fibras elásticas foi significativamente menor na PIU idiopática do que na PIU-ES.

Conclusões: A síntese aumentada de colágeno, a destruição de fibras elásticas, a alta proliferação miofibroblástica e a microvascularização diminuída podem representar um processo de remodelamento encontrado na pneumonia intersticial idiopática, enquanto o reverso pode representar mais um processo de reparo na pneumonia intersticial associada à ES.

Descritores: Células epiteliais; Neovascularização patológica; Colágeno; Elastina; Pneumonia intersticial idiopática; Esclerose sistêmica.
Introduction

Pulmonary involvement occurs more frequently in systemic sclerosis (SSc) than in other collagen vascular disorders, representing a significant cause of morbidity and mortality in this patient population. The most common manifestation of pulmonary involvement in SSc is interstitial fibrosis, which occurs in approximately 80% of cases, and pulmonary arterial hypertension, which occurs in up to 15%. Many authors have shown that a number of histologic patterns of interstitial fibrosis associated with collagen vascular disorders have a better prognosis than does lone cryptogenic fibrosing alveolitis, also known as idiopathic pulmonary fibrosis.

The most recent modifications to the system of classifying the various types of idiopathic interstitial pneumonia (IIP) were made in 2002. The histologic pattern of nonspecific interstitial pneumonia (NSIP), now recognized as an IIP subgroup, has a prognosis intermediate between that of usual interstitial pneumonia (UIP) and that of other IIPs, such as desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease (ILD) and cryptogenic organizing pneumonia.

Although histologic patterns of NSIP and UIP are known to occur in SSc, their prevalence, as well as their relationship with clinical parameters, response to treatment, and prognosis, are poorly known. One group of authors classified histologic appearances of surgical lung biopsies performed in patients with SSc and found that NSIP was the most common histologic pattern in patients with SSc, although the outcome was linked more strongly to disease severity at presentation and serial carbon monoxide diffusing capacity trends than to histopathologic findings. Although the NSIP and UIP histologic patterns are similar for idiopathic or SSc pulmonary fibrosis (SSc-NSIP and SSc-UIP), recent studies have demonstrated that the latter has a better prognosis, and that the clinical features of SSc-NSIP and SSc-UIP generally improve with corticosteroid therapy. This finding is probably related to differences in the lung repair/remodeling process, as well as to the effects of the treatment given in an attempt to avoid irreversible damage and to increase survival.

Molecular markers in epithelial cells, myofibroblasts, endothelial cells and the extracellular matrix (collagen/elastic system fibers) are increasingly recognized as playing an important role in regeneration, repair and remodeling following lung injury. Variations in these markers might also explain differences in the pathogenesis of fibrotic lung diseases, either idiopathic or SSc-associated. We postulate that going back to basics will bring us new ideas for better understanding the pathophysiological differences between IIP and interstitial pneumonia associated with connective tissue diseases.

The aim of this study was to examine the parenchymal and extracellular matrix remodeling process in idiopathic and SSc-associated interstitial pneumonia, focusing on the UIP and NSIP histologic patterns.

Methods

Between 1980 and 2002, open lung biopsy specimens were obtained from 39 patients: 15 with idiopathic NSIP, 10 with idiopathic UIP, 5 with SSc-UIP and 9 with SSc-NSIP, according to the criteria outlined by the Thoracic Society/European Consensus Group and American Rheumatism Association Diagnostic and Therapeutic Criteria Committee.

The biopsy specimens were reviewed independently by two pathologists. In most cases of discordance, a consensus was reached after a review by a third pathologist. For the remaining controversial cases, a consensus opinion was achieved by a final face-to-face meeting of the pathologists, all of whom were blinded to the clinical information.

Temporally homogenous septal inflammatory fibrotic thickening and epithelial cell proliferation were considered characteristic of NSIP. The UIP pattern was characterized as alternating areas of normal parenchyma, alveolar collapse, honeycombing and severe mural organizing fibrosis, defined as sites of active remodeling overlying fibrous airspace walls, indicative of temporal heterogeneity, or overlying normal rigid pulmonary structures (interlobular septa) in the form of fibroblast foci and granulation tissue.

In the lung parenchyma, epithelial cells, endothelial cells and myofibroblasts were evaluated through immunohistochemical staining using the avidin–biotin immunoperoxidase complex technique. For epithelial cells, the antibodies used were anti-cytokeratin 7 (anti-CK7,
Systemic sclerosis and idiopathic interstitial pneumonia: histomorphometric differences in lung biopsies

Figure 1 - Histologic representation of idiopathic NSIP and SSc-NSIP. Immunoexpression of CK7 in the continuous basement membrane in idiopathic NSIP (a) and SSc-NSIP (b). SP-A-positive epithelial cells are more numerous in idiopathic NSIP (c) than in SSc-NSIP (d). Myofibroblasts present higher expression of α-SMA in idiopathic NSIP (e) than in SSc-NSIP (f). Small capillary vessels are sparse in idiopathic NSIP (g) and dense in SSc-NSIP (h). Immunostaining: for CK7 (a and b, ×100); for SP-A (c and d, ×100); for α-SMA (e and f, ×100); and for CD34 (g and h, ×100). CK7: cytokeratin 7; SP-A: surfactant protein A; α-SMA: alpha smooth muscle actin; NSIP: nonspecific interstitial pneumonia; SSc: systemic sclerosis; and UIP: usual interstitial pneumonia.
Figure 2 - Histologic representation of idiopathic UIP and SSc-UIP. Similar immunoeexpression of CK7 in idiopathic UIP (a) and SSc-UIP (b); similar immunoeexpression of SP-A in idiopathic UIP (c) and SSc-UIP (d). In areas of mural organization (stars) and alveolar collapse (arrows), proliferation of highly active myofibroblasts can be seen overlying the original surface of the airspace in idiopathic UIP (e) when compared with SSc-UIP (f). Immunoeexpression of different vascular markers in idiopathic and SSc-UIP. Minimal immunoeexpression of the endothelial cell marker (CD34) in idiopathic UIP (g) when compared with SSc-UIP (h). Immunostaining: for CK7 (a and b, ×100); for SP-A (c and d, ×100); for α-SMA (e and f, ×100); and for CD34 (g and h, ×100). CK7: cytokeratin 7; SP-A: surfactant protein A; α-SMA: alpha smooth muscle actin; NSIP: nonspecific interstitial pneumonia; SSc: systemic sclerosis; and UIP: usual interstitial pneumonia.
Figure 3 – Strong, homogeneous red-orange birefringence in the interstitium in idiopathic NSIP (a), contrasting with the low red-orange birefringence observed in SSc-NSIP (b). Elastic fiber density is lower in idiopathic NSIP (c) than in SSc-NSIP (d). Strong, heterogeneous red-orange birefringence found in the interstitium in idiopathic UIP (e), contrasting with the low red-orange birefringence observed in SSc-UIP (f) and low red-orange birefringence is observe in idiopathic UIP (g) when compared with SSc-UIP (h). Picrosirius-polarization (a, b, e and f, ×100); and Weigert’s resorcin-fuchsin (c, d, g and h, ×100). NSIP: nonspecific interstitial pneumonia; SSc: systemic sclerosis; and UIP: usual interstitial pneumonia.
10 fields per biopsy when the distribution of the lesions were homogeneous, as in the NSIP histologic pattern, whereas we quantified 30 fields per biopsy in cases of UIP: 10 in normal areas; 10 in intermediate areas (alveolar collapse); and 10 in remodeling areas (mural fibrosis and honeycombing areas). We averaged the microscopic fields to obtain the final percentage of stained structures.

The extracellular matrix was evaluated for collagen/elastic fibers by histochemical staining. Collagen fiber characterization was performed using 0.2% solution of Sirius red (Direct Red 80; C. I. 35780; Aldrich, Milwaukee, WI, USA) dissolved in aqueous saturated picric acid. The enhancement of collagen birefringence promoted by the Picrosirius-polarization method is specific for collagenous structures composed of aggregates of oriented molecules. Elastic fibers were characterized using Weigert’s resorcin-fuchsin method, after oxidation. This method allows the selective identification of the three types of elastic system fibers (oxytalan; elaunin; and fully developed elastic fibers).

The quantification of collagen/elastic fibers in interstitial walls was performed using an image analysis system. The system consists of an Olympus camera, coupled to an Olympus microscope. Positive epithelial cells (CK7 and SP-A), endothelial cells (CD34) and myofibroblasts (α-SMA) were analyzed without image analysis, since the eyepiece-only method is more specific for quantifying the structures and forms that would present similar densities in the image analysis. In brief, we used a 400x eyepiece containing a systematic point-sampling grid with 100 points and 50 lines in order to count the fraction of lines overlying positively stained structures. In the UIP histologic pattern, the temporal heterogeneity and alternating areas of remodeling represented three different areas in the same biopsy. As usual, we quantified

### Table 1 - Descriptive analysis of the cases evaluated.

<table>
<thead>
<tr>
<th>Group</th>
<th>Marker</th>
<th>CK7</th>
<th>SP-A</th>
<th>α-SMA</th>
<th>CD34</th>
<th>Collagen</th>
<th>Elastic</th>
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<tr>
<td></td>
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<td>%, mean ± SEM</td>
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<tr>
<td>Idiopathic NSIP [n = 15]</td>
<td>CK7</td>
<td>11.45 ± 0.90</td>
<td>7.02 ± 0.74</td>
<td>8.07 ± 0.57</td>
<td>7.97 ± 0.58</td>
<td>14.46 ± 0.77</td>
<td>7.25 ± 0.81</td>
</tr>
<tr>
<td>SSc-NSIP [n = 9]</td>
<td>SP-A</td>
<td>4.62 ± 0.64</td>
<td>4.03 ± 0.97</td>
<td>9.83 ± 0.39</td>
<td>8.95 ± 0.72</td>
<td>9.82 ± 0.79</td>
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<tr>
<td>Idiopathic UIP [n = 10]</td>
<td>α-SMA</td>
<td>12.78 ± 1.2</td>
<td>3.97 ± 0.32</td>
<td>20.54 ± 1.38</td>
<td>5.73 ± 0.90</td>
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<tr>
<td>SSc-UIP [n = 5]</td>
<td>CD34</td>
<td>9.43 ± 0.91</td>
<td>5.49 ± 0.44</td>
<td>14.47 ± 0.73</td>
<td>8.72 ± 0.78</td>
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<td></td>
<td>Collagen</td>
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<td>Elastic</td>
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<td>Comparison</td>
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<tr>
<td>Idiopathic NSIP vs. SSc-NSIP</td>
<td>CK7</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
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<tr>
<td>Idiopathic NSIP vs. Idiopathic UIP</td>
<td>SP-A</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<tr>
<td>Idiopathic NSIP vs. SSc-UIP</td>
<td>α-SMA</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<tr>
<td>SSc-NSIP vs. Idiopathic UIP</td>
<td>CD34</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<tr>
<td>Idiopathic UIP vs. SSc-UIP</td>
<td>Collagen</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
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<td>Elastic</td>
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CK7: cytokeratin 7; SP-A: surfactant protein A; α-SMA: alpha smooth muscle actin; NSIP: nonspecific interstitial pneumonia; SSc: systemic sclerosis; and UIP: usual interstitial pneumonia.
Results

The NSIP pattern was characterized by temporally homogenous thickening of the alveolar septa by fibroblasts embedded in an edematous stroma. The fibroblasts in septal thickening due only to inflammation did not show the contractile myofibroblast phenotype as in mural fibrosis of UIP, representing areas of interstitial reaction with no damage to the basement membrane. This was confirmed by the continuous basement membrane underlying CK7 and SP-A-positive epithelial cells (Figure 1).

The UIP pattern was characterized by alternating areas of normal parenchyma, alveolar collapse, honeycombing, and severe mural organizing fibrosis. In areas of alveolar collapse, proliferation of highly active myofibroblasts was observed overlying the original surface of the airspace (Figure 2). There were no epithelial cells overlying the myofibroblasts. We observed only a few inflammatory cells and thin collagen fibers, among which we observed neither vascular structures nor elastic fibers. In the honeycombing areas, CK-positive/SP-A-negative epithelial cells recovered the focus of mural fibrosis (Figure 2). The myofibroblasts showed less expression of α-SMA and assumed the characteristic appearance of fibroblast foci. Thin collagen fibers were more abundant, without the thick counterpart, and thin elastic fibers were occasionally noted (Figure 3). The adjacent airspace wall showed prominent SP-A-positive pneumocytes or bronchiolar epithelial recovery. Mural organizing fibrosis areas demonstrated a continuous epithelial lining with scattered SP-A-positive cells overlying the basement membrane.

Mesenchymal cells displayed a spindle configuration and focal α-SMA expression. Thick collagen fibers and thin elastic fibers were observed running parallel to the surface, settling the tissue by apposition, and occasional small capillary vessels were detected. Healed sites showed complete original epithelial lining overlying a continuous basement membrane. The subjacent stroma was poorly vascularized and consisted of α-SMA-negative fibroblasts, thick collagen bundles, and irregularly arranged thin and thick frayed elastic fibers (Figure 3). The adjacent airspace wall was also lined by the original epithelium. Mural fibrosis was observed most commonly in the healing phase.
There were no statistical differences between the idiopathic forms and the SSc-associated forms in terms of the CK7-positive epithelial cell counts (Table 1 and Figure 4a). However, the percentage of SP-A-positive epithelial cells was significantly greater in idiopathic NSIP than in SSc-NSIP (7.02 ± 0.74 vs. 4.62 ± 0.64; p = 0.01; Table 1 and Figure 4b), as well as being significantly greater in idiopathic UIP than in SSc-UIP (p = 0.02).
Idiopathic NSIP presented significantly higher percentages of α-SMA-positive cells than did SSc-NSIP (7.88 ± 0.57 vs. 4.63 ± 1.23; p = 0.01). The percentages of α-SMA-positive cells were also significantly greater in idiopathic UIP than in SSc-UIP (12.78 ± 1.27 vs. 9.68 ± 1.61; p < 0.001; Figure 4c).

As can be seen in Figure 4d, the percentages of CD34-positive endothelial cells in the pulmonary microvasculature were comparable between idiopathic NSIP and SSc-NSIP (8.01 ± 0.54 vs. 9.33 ± 0.28; p > 0.05), although these values were lower in idiopathic UIP than in SSc-UIP (3.97 ± 0.32 vs. 5.30 ± 0.81; p < 0.001).

The density of collagen fibers was significantly higher in idiopathic NSIP and UIP (14.00 ± 0.84 and 20.54 ± 1.38; p = 0.002) than in SSc-NSIP and UIP (8.84 ± 1.06 and 14.77 ± 0.98; p < 0.001, as can be seen in Table 1 and Figure 4c. In contrast, the elastic fiber density was lower in idiopathic NSIP than in SSc-NSIP (7.41 ± 0.75 vs. 10.06 ± 1.13), although the difference was not statistically significant (p = 0.07; Table 1 and Figure 4f). A significant difference in elastic fiber density was found between idiopathic UIP and SSc-UIP (5.73 ± 0.90 vs. 9.57 ± 1.01; p = 0.009).

In idiopathic NSIP and idiopathic UIP, a positive correlation was found between epithelial and endothelial cells (r = 0.70; p < 0.01), whereas epithelial cells were found to correlate negatively with myofibroblasts (r = -0.52; p < 0.01) and collagen fibers (r = -0.44; p = 0.002). Myofibroblasts correlated negatively with endothelial cells (r = -0.70; p < 0.01), negatively with elastic fibers (r = -0.31; p = 0.03) and positively with collagen fibers (r = 0.73, p < 0.01). Endothelial cells correlated negatively with collagen fibers (r = -0.70, p < 0.01). A negative correlation was found between collagen fibers and elastic fibers (r = -0.41; p < 0.01).

**Discussion**

The present study examined the parenchymal and extracellular matrix remodeling processes in the UIP and NSIP histologic patterns of idiopathic and SSc-associated interstitial pneumonia. We found differences among these groups in specialized epithelial and myofibroblast cell populations. For example, activation of specialized SP-A-positive epithelial cells and myofibroblasts was greater in the idiopathic forms. It is of note that the percentages of CD34-positive endothelial cells in the pulmonary microvasculature were comparable between the two NSIP patterns, whereas it was lower in idiopathic UIP than in SSc-UIP. In addition, both idiopathic groups presented increased collagen fiber density, although elastosis was only observed in idiopathic UIP.

The process of pulmonary remodeling undoubtedly involves a complex and dynamic interplay among parenchymal and interstitial constituents. Among these, the epithelium, the microvasculature and the extracellular matrix are thought to be important because they are responsible for the architectural integrity. For example, alveolar collapse has been described as an important form of active remodeling in diffuse alveolar damage.\(^{[20]}\)

The destruction of the epithelial lining and the apposition of two denuded septa are followed by re-epithelialization of the air-exposed surface, leading to permanent loss of alveoli. In our study, SP-A-positive epithelial cell counts were significantly higher in idiopathic NSIP than in SSc-NSIP, indicating that the proliferation of type II pneumocytes to re-epithelialize the denuded basement membrane is more regenerative in idiopathic NSIP, suggesting greater disruption of the basement membrane and adequate substrate for initiating the intra-alveolar fibrogenic process. In fact, we found similar numbers of SP-A-positive cells in idiopathic UIP, also indicating a severe degree of alveolar collapse. This finding is in line with those of other authors.\(^{[21]}\)

We also demonstrated that α-SMA-positive cell counts were significantly higher in idiopathic NSIP than in SSc-NSIP, as well as being higher in idiopathic UIP than in SSc-UIP. These findings in the idiopathic histologic pattern probably reflect what occurs in the alveolar spaces after extensive epithelial basement membrane denudation by necrosis and sloughing of type I pneumocytes, as previously reported.\(^{[22]}\)

Proliferating intraluminal fibroblasts have a contractile phenotype, presenting SMA-type filaments in their cytoplasm,\(^{[23,24]}\) and represent the main source of collagen production.\(^{[25]}\) Ultrastructural studies have demonstrated that, during the incorporation of intra-alveolar fibrosis, these myofibroblasts attach to the luminal surface of the epithelial basement.
and lower microvascular density could contribute to the more rapid progression in idiopathic diseases.

The collagen and elastic systems, the major fibrous components of the extracellular matrix, have been addressed in previous reports on IIP, in an attempt to establish a correlation between alterations in their content and possible deleterious consequences for pulmonary function. Several studies previously carried out by our group have shown that lung collagen and elastic contents are increased in both acute and chronic ILDs, demonstrating that significant remodeling of the alveolar structure occurs in these situations. In the present study, we demonstrated that the density of collagen fibers was significantly greater in both forms of IIP (NSIP and UIP), although low elastic fiber density was mainly found in idiopathic NSIP.

The low microvascularization, as well as the increased deposition of collagen fibers (organizing fibrosis) and destruction of elastic fibers, in idiopathic UIP and idiopathic NSIP are thought to maintain the activity of the process and might prevent resolution; the capillary network diminishes progressively from the early to the late phase, whereas the opposite occurs in incorporating fibrosis. In fact, establishing a vascular supply is a sine qua non requisite for any newly formed viable tissue (proliferative phase endometrium, neoplastic tissues, etc.) and its absence is synonymous with atrophy. In the present study, we confirmed that direct epithelial integrity is important to maintaining tissue homeostasis mainly in idiopathic NSIP and UIP, whereas the integrity of endothelial (CD34-positive) cells is crucial for tissue architecture in SSc-NSIP and SSc-UIP.

In summary, we found that the parenchymal and extracellular remodeling process in SSc-associated interstitial pneumonia is different from that occurring in IIP. Increased collagen synthesis, destruction of elastic fibers, high myofibroblast proliferation and poor microvascularization might represent a more definitive remodeling process in IIP, whereas the reverse might represent a repair process in SSc-associated interstitial pneumonia. These two different forms of parenchymal repair might represent different adaptive responses to injury in these forms of ILD.
Acknowledgments

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