Phenotype of regenerative epithelium in idiopathic interstitial pneumonias

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The epithelial alteration in interstitial pneumonias is one of the repair processes at the sites of disease activity. Regenerative epithelial cells may participate in remodeling of the lung. To determine the phenotype of regenerative epithelial cells in usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP), the expression of Clara cell 10KD protein (CC10), cytokeratin (CK) 14 and 17, surfactant apoprotein (SP)-A, KL-6/MUC1, transforming growth factor (TGF) β₂ were examined in 25 patients with UIP, 9 patients with NSIP and normal lung tissues from 10 patients with lung cancer.

In honeycomb lesions of UIP, non-ciliated columnar cells mainly expressed CC10, cuboidal cells expressed CC10, CK17, CK14 and SP-A in descending order.

Fibroblastic foci are covered by CK17, CK14, CC10, and a few SP-A positive flattened or cuboidal cells. Regenerative epithelium in NSIP mainly comprised cuboidal cells expressing SP-A, CC10 and CK17. KL-6 was more remarkably expressed in cuboidal and non-ciliated columnar cells both in UIP and NSIP. Expression of TGFβ₂ was observed in cuboidal and flattened epithelium.

In severe fibrotic areas, CC10 expressing cells were more prominent, while SP-A positive cells were more prominent in less fibrotic areas.

Regenerative epithelial cells in remodeling area in UIP may be derived from bronchiolar basal cells and Clara cells, while most of those in NSIP may be derived from type II pneumocytes. The different origin of regenerative epithelium may reflect the severity and extent of the injury and the degree of consequent fibrosis in UIP and NSIP.

Key words: Regenerative epithelium, phenotype, bronchiolar basal cell, UIP, NSIP

Introduction

Among the idiopathic interstitial pneumonias (IIPs), idiopathic pulmonary fibrosis (IPF) is the most frequent chronic fibrosing interstitial pneumonia, which histologically shows a usual interstitial pneumonia (UIP) pattern. The histologic hallmarks and chief diagnostic criteria of UIP are a heterogeneous appearance of the fibrotic areas with alternating areas of normal lung, scattered fibroblastic foci, and honeycomb change.⁴,⁵ Nonspecific interstitial pneumonia (NSIP) has a broad spectrum of histologic findings comprising cellular and fibrosing patterns and has a significantly better prognosis than that of IPF.⁴,⁵ The pathological diagnosis of UIP and NSIP is primarily based on distribution and temporal appearance of inflammation and fibrosis, and remodeling of alveoli.⁴,⁵ The histological alterations of interstitial pneumonias consist of the injury and repair at the disease activity, and it is important to
know whether the lesions are ongoing or steady for treatment and prognosis.

The epithelial alteration in the interstitial pneumonias is one of the repair processes at the sites of disease activity. Type II pneumocytes and regenerative epithelial cells produce various chemoattractants for fibroblasts and may participate in the fibrosing process of interstitial pneumonias.\(^6,7\)

Areas of honeycomb change are composed of cystic remodeling air spaces that are frequently lined with metaplastic bronchiolar epithelia or hyperplastic alveolar pneumocytes, and occasionally metaplastic squamous epithelium.\(^1,4\) The phenotype of regenerative epithelium is considered to be changeable, depending upon the new insults during the progression or restoration of the disease. As for the morphological phenotype of epithelial cells of fibrotic lung disorders, Kawanami et al. reported that type II cells proliferate mainly in the areas with less severe degrees of fibrosis, cuboidal cells are heterogeneous, comprising bronchiolar basal cells, and respiratory bronchioles become the main source of epithelial renewal in areas of very severe lung damage.\(^8\) Regarding the immunohistochemical phenotype of UIP, Iyonaga et al. reported various cytokeratin (CK) expression in the regenerative epithelium of IPF.\(^9\) They suggested that the regenerative epithelial cells are altered population and may play an important role in the progression of chronic inflammation in IPF.

It has been reported that Clara cells may aid bronchiolar repopulation following the injury.\(^10\)\(^-\)\(^12\) Secretory protein specific for Clara cells is identified as Clara cell 10KD protein (CC10).\(^15\) Surfactant apoprotein (SP)-A is hydrophilic glycoprotein, and secreted by type II pneumocytes.\(^14\) KL-6 is a high molecular weight glycoprotein and classified as “cluster 9 (MUC1)” of lung tumor,\(^15\) and useful indicator of disease activity in patients with interstitial pneumonias.\(^16\) It has been reported that KL-6 was expressed in regenerative type II pneumocytes of interstitial pneumonias.\(^16\) As for fibrosis in the lung, transforming growth factor (TGF)/β can regulate cell growth and differentiation as well as stimulation of fibroblasts to synthesize collagen, fibronectin, proteoglycans, and other proteins of the extracellular matrix, and participates in the fibrotic process in interstitial lung disease.\(^17,18\)

This study intends to 1) clarify the phenotype of regenerative epithelial cells in UIP and NSIP at the sites of disease activity using the immunohistochemical analysis, and 2) compare the pathological status of UIP and NSIP, referring the correlation between regenerative epithelial cells and the degree of fibrosis as the activity of the disease.

### Material and methods

We examined 25 cases of IPF/UIP (22 males and 3 females) and 9 cases of NSIP (6 males and 3 females) by video-assisted thoracoscopic lung biopsy and surgical resection at the Japanese Red Cross Medical Center in Tokyo between 1990 and 2002. The twenty-five cases of IPF/UIP consisted of 9 cases of IPF/UIP without lung cancer and 16 cases of UIP associated with lung cancer. The average age of patients with IPF/UIP was 63±9 years, NSIP was 64±10 years, and the average smoking index (cigarettes/day, years) for IPF/UIP was 1254±963, and NSIP was 1486±953. The diagnosis of UIP and NSIP was made according to ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias, 2002.\(^1\) The diagnosis of IPF/UIP was confirmed based on clinical symptoms such as dyspnea on exertion and dry cough, reduced pulmonary function, reticulonodular shadow on chest X-ray and CT, high levels of serum SP-A, SP-D and KL-6, and histopathology of UIP.\(^3,5,6\) However, as the data for SP-D and KL-6 were available only in the several cases, we do not compare these serum data with histopathology in this study. NSIP was confirmed based on typical bilateral pulmonary interstitial infiltration showing as an opaque ground glass shadow on chest X-ray and CT, other clinical symptoms similar to those for IPF/UIP, and histopathology of diffuse, temporally homogeneous interstitial infiltrates and fibrosis.\(^5,15\) In this study, 7 cases of NSIP are classified as group II and 2 cases as group III, according to Katzenstein.\(^15\) Any cases of NSIP are not associated with collagen vascular disease from serological data.

We also examined 10 cases of normal lung tissue without IPF or other chronic lung diseases, which were taken well away from the primary lung cancer and examined as controls. They were 6 males and 4 females with a mean age of 65±9 years and an average smoking index of 1000±910.

All the lungs were fixed in 10% buffered formalin and embedded in paraffin. All paraffin sections were routinely stained with hematoxylin-eosin, elastica van Gieson, Masson-trichrome and periodic acid-schiff-alcan blue.

For immunohistochemical analysis of regenerative epithelial cells, we used polyclonal antibodies against...
CC10 and TGF\(\beta_2\), and monoclonal antibodies against CK17, CK14, SP-A and KL-6. The antibodies and sources are given in Table 1. Paraffin-embedded, 4\(\mu\)m-thick sections were deparaffinized in xylene and rehydrated. They were washed in phosphate-buffered saline (PBS) with 0.01% Tween 20, and incubated for 30 minutes in 0.3% H\(_2\)O\(_2\) in methanol to inactivate endogenous peroxidase. For antigen retrieval, the sections were digested with 0.05% trypsin for 30 minutes at room temperature or 0.1% hyaluronidase at 37°C for 30 minutes, or heated in a microwave oven at 500w for 15 minutes in a 10mM sodium citrate buffer at pH6.0. Then the sections were incubated at 4°C overnight with the primary antibodies, then the secondary antibody, biotinylated goat antimouse IgG or antirabbit IgG (DAKO Japan, Kyoto, Japan) was applied for 30 minutes at room temperature. After washing three times in PBS, they were reacted with peroxidase-conjugated streptavidin (0397, DAKO Japan, Kyoto, Japan). Finally, the reaction products were visualized with 0.02% 3,3' dianobenzidine (DAB) in a 0.1 mol/L Tris-HCl buffer, pH7.6, in 0.005% H\(_2\)O\(_2\) for 5 minutes, and lightly counter-stained with hematoxylin. Negative controls consisted of a non-immune, isotype-matched monoclonal antibody. The same immunohistochemical study was performed in normal controls.

To evaluate the heterogeneity of regenerative epithelial cells we counted the positive cells for CC10, CK17, CK14, SP-A, KL-6 and TGF\(\beta_2\) in the unit area (mm\(^2\)) in UIP and NSIP cases, using an Olympus micrometer with a \(\times20\) objective lens in four representative areas with fibrotic remodeling in each case. The whole epithelial cells in the unit area (mm\(^2\)) correspond to the parent population of the cells. The percentage of positive cells was counted in each section and presented as mean±standard deviation. Among the regenerative epithelial cells, we focused on cuboidal cells and counted them in three types, because they frequently appear in fibrotic process in interstitial pneumonias.

To determine the relationship between regenerative epithelial phenotype and fibrosis, we counted the positive cells for CC10, CK17, SP-A, KL-6 and TGF\(\beta_2\) in the determined areas of fibrosis using the grading of Ashcroft,\(^20\) and expressed them as percentage. Criteria for grading lung fibrosis by Ashcroft: histological features of fibrosis score of grade 0 was normal lung, grade 1 to 2 was minimal fibrous thickening of alveolar or bronchiolar walls, grade 3 to 4 was moderate thickening of walls without obvious damage to lung architecture, grade 5 to 6 was increased fibrosis with definite damage to lung structure and formation of fibrous bands or small fibrous masses, grade 7 to 8 was severe distortion of structure and large fibrous areas and honeycomb lesion is placed in this category. The statistical analysis was performed by the Mann Whitney test, and \(p\) values less than 0.05 were considered significant.

<table>
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<td>Trypsin</td>
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<td>TGF(\beta_2)</td>
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<td>Hyaluronidase, Microwave</td>
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R: rabbit polyclonal, M: mouse monoclonal
Results

1. Immunohistochemical analysis

Normal lung tissues
1) Expression of CC10, CK17, CK14 and SP-A.

In the bronchiolar epithelium, CC10 was intensely expressed in the cytoplasm of Clara cells in a uniform staining pattern and some of the basal cells [Fig. 1a]. CK17 was constantly expressed in basal cells, while CK14 expressed in some of the basal cells of bronchiole [Fig. 1b, c]. SP-A was strongly granular-positive in type II pneumocytes [Fig. 1d].

2) Expression of KL-6 and TGF\(\beta_2\).

KL-6 was strongly expressed in the apical portion and uniformly expressed in the cytoplasm of Clara cells and some of the basal cells of bronchiole [Fig. 2a], and also in the cytoplasmic membrane and cytoplasm of type II pneumocytes [Fig. 2b]. Occasionally, KL-6 was co-expressed in CC10 positive non-ciliated columnar cells. TGF\(\beta_2\) was expressed in some of the non-ciliated columnar cells, basal cells of the bronchiole [Fig. 2c] and alveolar macrophages whereas type II pneumocytes were negative to TGF\(\beta_2\).

Fibrotic lung tissues
1) UIP cases.

(1) Expression of CC10, CK17, CK14 and SP-A.

Fibrous areas showed a patchy distribution at the subpleural and periphery of the lobules. Honeycomb lesions were characterized by irregularly dilated air-}

![Image](image_url)
spaces that were lined by bronchiolar columnar, cuboidal, flattened and occasionally squamous metaplastic epithelium [Fig. 3a]. Honeycomb lesions were detected in 22 of 25 cases (88%) of UIP, while microscopic small honeycomb lesion was seen in 1 of 9 cases (11.1%) of NSIP.

In honeycomb lesion, CC10 was intensely expressed in the cytoplasm of non-ciliated columnar epithelial cells [Fig. 3b]. CC10-positive non-ciliated columnar epithelial cell occupied an average of 50% of the lining epithelium in the honeycomb lesion (Table 2). The cuboidal cells of the lining epithelium in the honeycomb lesion were divided into three phenotypes; CC10-positive, CK-17 and CK-14-positive and SP-A-positive cells [Fig. 3c] in descending order. But each incidence was less than 25% (Table 2). A few of the non-ciliated columnar epithelial cells co-expressed CC10 and SP-A in honeycomb areas [Fig. 3b]. Some of the basal cells of bronchiolar metaplastic epithelium expressed CC10, CK14 and CK17 [Fig. 3d]. Flattened epithelium were occasionally observed in the honeycomb lesion, which were positive for CC10, CK14, CK17 and SP-A, in random distribution. Squamous metaplastic epithelial cells intensely expressed CK14 and CK17 (Table 2).

Fibroblastic foci was detected in 80% of the UIP cases. They were sparsely distributed in the margin of dense fibrosis of the periphery of the lobule and honeycomb lesion. They were usually lined by flattened or cuboidal cells [Fig. 3a]. Flattened cells usually expressed CK17, CK14 and CC10, while cuboidal cells expressed CC10 and CK17. CK17 and CC10-positive cells each occupied an average of 50% and 20% of the lining epithelium in the fibroblastic foci. Occasionally, CC10 positive cuboidal cells were overlying CK17 positive cells [Fig. 3e]. Rarely, SP-A was expressed in cuboidal cells in the fibroblastic foci.

(2) Expression of KL-6 and TGFβ2.

In honeycomb lesion, KL-6 was strongly expressed in the cytoplasm and apical portion of non-ciliated columnar and cuboidal cells [Fig. 4a]. KL-6 positive cells occupied an average of 75% of the lining epithelium (Table 2). KL-6 was expressed in flattened epithelial cells and some of the basal cells in honeycomb lesion [Fig. 4a]. Some of the non-ciliated and cuboidal cells co-expressed CC10 and KL-6. KL-6 was also expressed flattened and cuboidal epithelial cells in fibroblastic foci [Fig. 4b].

In honeycomb lesion, TGFβ2 was expressed mainly in cuboidal and flattened epithelial cells, occasionally in some of the non-ciliated columnar epithelial cells,
squamous metaplastic epithelial cells and some of the metaplastic bronchiolar basal cells [Fig. 4c]. In fibroblastic foci, flattened and cuboidal cells also expressed TGFβ2 [Fig. 4d].

2) NSIP cases

(1) Expression of CC10, CK17, CK14 and SP-A.
NSIP revealed relatively less structural remodeling with proliferation of cuboidal epithelial cells and flattened epithelial cells [Fig. 5a]. Cuboidal epithelial cells was divided into three phenotypes; i.e., SP-A-positive cells were the most prominent [Fig. 5b], and CC10-positive, CK14 and CK17-positive cells were less than 25%. CC10-positive cuboidal cells were sparse and usually appeared close to the bronchiole [Fig. 5c]. Some of the flattened epithelial cells in the mural incorporation expressed CC10, CK17, and SP-A.

(2) Expression of KL-6 and TGFβ2.
KL-6 was strongly expressed in cuboidal and flattened epithelial cells [Fig. 5d]. CC10 and KL-6 were co-expressed in some cuboidal epithelial cells. Occasionally, TGFβ2 was expressed in cuboidal and flattened epithelial cells [Fig. 5e]. The phenotypes of regenerative epithelial cells in fibrotic lung tissues from patients with UIP and NSIP are summarized in Table 2.

2. Correlation between regenerative epithelial phenotype and fibrosis in UIP and NSIP pattern.
The grading of fibrosis in each of the lung section was scored on a scale from 0 to 8, according to Ashcroft. Fibrosis scores of grade 5 to 6 and grade 7 to 8 were recognized in the 25 cases of UIP, grade 3 to 4 was recognized in the 25 cases comprising 16 UIP and 9 NSIP.

Most of the cases with UIP had fibrosis scores of grade 7 to 8, with NSIP scores of grade 3 to 4. The incidence of various phenotypes of regenerative epithelial cells and grade of fibrosis are shown in Figure 6. The percentage of positive cells for CC10 was significantly higher in the fibrosis score of grade 7 to 8 (p<0.005) and 5 to 6 (p<0.05) areas, than in the fibrosis score of grade 3 to 4 areas. The percentage of positive cells for SP-A in UIP was significantly higher in the fibrosis score of grade 3 to 4 areas, than in the fibrosis score of grade 5 to 6 (p<0.005) and 7 to 8 (p<0.0001) areas. The percentage of positive cells for KL-6 was significantly higher in the 2 groups with fibrosis score of grade 3 to 6 areas, than in the fibrosis score of grade 7 to 8 areas (p<0.0001).

Positive cells for CC10 and CK17 proliferated mainly in the more fibrotic areas, while SP-A and KL-6-positive cells proliferated mainly in the relatively less fibrotic areas. Further, the percentage of TGFβ2 positive cells was significantly higher in fibrosis score of grade 7 to 8 than in fibrosis score of grade 3 to 4 (p<0.0001).

In fibrosis score of grade 3 to 4, the percentage of positive cells to CC10, CK17, SP-A, KL-6 and TGFβ2...
Fig. 3. Expression of CC10, CK17 and SP-A in UIP.
(a) Honeycomb lesion was lined by bronchiolar columnar, cuboidal and flattened epithelium, and fibroblastic focus (arrow) lined by cuboidal and flattened epithelium. (HE)
(b) CC10 (brown) was strongly expressed in non-ciliated columnar epithelial cells, and SP-A (blue) was expressed in some of the non-ciliated columnar cells, also a few of the non-ciliated columnar epithelial cells co-expressed CC10 and SP-A in the honeycomb lesion.
(c) SP-A (brown) was expressed in some of the cuboidal cells in the honeycomb lesion.
(d) CC10 (brown) was strongly expressed in non-ciliated columnar cells, and CK17 (blue) was strongly expressed in basal cells of the bronchiolar metaplastic epithelium in the honeycomb lesion.
(e) CC10 (brown) positive cuboidal cells were overlying CK17 (blue) positive cells of lining epithelium of the fibroblastic focus.
Discussion

The present immunohistochemical study demonstrated more heterogeneous appearance of phenotypes of regenerative epithelial cells in the fibrotic areas of UIP than in those of NSIP. Although the fibrous areas in UIP show temporal heterogeneity, this study demonstrated heterogeneity of phenotypes of regenerative epithelial cells in the remodeling areas. The regenerative epithelium in the honeycomb lesion and fibroblastic foci consisted of CC10-positive cells, CK17, CK14-positive cells and a few SP-A-positive cells. In the honeycomb lesion, CC10-positive cells were the most prominent. CC10-positive cells comprised non-ciliated columnar, cuboidal and occasionally flattened cells in the honeycomb lesion and fibroblastic foci of UIP. CC10 is specific for Clara cells, which has been recognized as progenitor cells of the bronchiolar epithelium, and contribute to repopulation after injury. CC10 has been reported as a candidate for controlling inflammatory events in the lung, and inhibits platelet-derived growth factor (PDGF)-induced chemotaxis of lung fibroblasts in a dose-
Fig. 5. Expression of SP-A, CC10, KL-6 and TGFβ in NSIP.
(a) Proliferation of cuboidal epithelial cells in the alveolar walls. (HE)
(b) SP-A was strongly expressed in cuboidal epithelial cells in a granular staining pattern.
(c) CC10 was expressed in some of the cuboidal cells, was appeared close to the bronchiole.
(d) KL-6 was strongly expressed in cuboidal epithelial cells remarkably at the apical portion.
(e) TGFβ was expressed in cuboidal epithelial cells.
dependent manner, and a decreased availability of CC10 may facilitate the recruitment of fibroblasts in fibrosing lung disorders. Subpopulation of CC10-expressing cells may importantly contribute to regeneration after various injury. Cuboidal cells are characteristic pattern of regenerative epithelial cells, which usually appear in interstitial lung disorders. Electron microscopic study by Kawanami revealed two types of cuboidal cells, one derived from bronchiolar basal cells and the other from cuboidal cells in the respiratory bronchioles.

In UIP, cuboidal cells in honeycomb lesion may be divided into CC10(+)(SP-A(-)), CK14(+)SP-A(-), CK17(+)SP-A(-), and SP-A(+) cells. In fibroblastic foci, CK17(+)SP-A(-), CK14(+)SP-A(-), CC10(+)SP-A(-) and CK14(-) CK17(-)/SP-A(+) cuboidal and flattened cells are observed. In NSIP, cuboidal cells may be divided into SP-A(+)CK17(-) or CK14(-) hyperplastic type II pneumocytes, CC10(+)SP-A(-), CK17(+)/SP-A(-) and CK14(+)/SP-A(-) cells. The latter two revealed phenotype of bronchiolar basal cells, which may be derived from bronchiolar basal cells as reported by Iyonaga.

Fibroblastic foci in UIP are considered to form young reparative lesions due to new insults occurring in the remodeling fibrotic area in UIP. CC10-positive cuboidal cells overlying CK17-positive cells in fibroblastic foci suggest that CK17-positive cells appear in the early phase and then CC10-positive cells cover them. CK17-positive bronchiolar basal cells may contribute to the initial repair. CK17 or CK14 and CC10-positive flattened cells may be the stem cell population in the remodeling areas of chronic interstitial lung disorders and some of them may develop to SP-A expressing cells.

In UIP, regenerative epithelial cells reveal bronchiolar phenotype, while in NSIP, most of those reveal phenotype of type II pneumocyte. The bronchiolar phenotype or type II pneumocyte of regenerative epithelial cells may reflect the severity and extent of the injury of the

<table>
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<th>Grade of fibrosis</th>
<th>(UIP=16, NSIP=9)</th>
<th>(UIP=25)</th>
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<td>Frequency of positive cells, %</td>
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* p<0.005 CC10-positive cells(%) in the fibrosis score of grade 7 to 8 vs grade 3 to 4.
** p<0.05 CC10-positive cells(%) in the fibrosis score of grade 5 to 6 vs grade 3 to 4.
+ p<0.0001 SP-A-positive cells(%) in the fibrosis score of grade 7 to 8 vs grade 3 to 4.
++ p<0.005 SP-A-positive cells(%) in the fibrosis score of grade 5 to 6 vs grade 3 to 4.
@@ p<0.0001 KL-6-positive cells(%) in the fibrosis score of grade 3 to 4 vs grade 7 to 8.
# p<0.0001 TGFβ2-positive cells(%) in the fibrosis score of grade 7 to 8 vs grade 3 to 4.

Fig. 6. Correlation between regenerative epithelial phenotype and grade of fibrosis in UIP and NSIP.
alveoli, which also may be associated with the degree of fibrosis. The frequency of phenotype of regenerative epithelium is different between less fibrous areas and fibrotic areas in UIP and NSIP. In the more fibrotic areas in UIP with grade 7 to 8 of Ashcroft’s fibrosis score, CC10-positive columnar cells are significantly predominant. CK17-positive cells are also detected in these areas. In these more fibrous areas, inflammatory infiltration is very mild. These fibrous areas in the periphery of the lobule in UIP with CC10 and CK17 positive regenerative cells may be reconstructed to the epithelial and stromal microenvironment of bronchiolar type, although the alterations of microvessels have not been studied.

Recently, KL-6, SP-A and SP-D have been reported to be sensitive, useful serum markers for the diagnosis and monitoring of patients with interstitial pneumonias. KL-6 has a property as a chemotactic factor for fibroblasts. The elevation of serum KL-6 reflects severe epithelial damage as well as alveolar wall capillary damage in acute and subacute interstitial lung disorders. This study clearly demonstrated that KL-6 was strongly positive to the regenerative cuboidal cells and non-ciliated columnar cells, while in the normal lung, KL-6 was positive to type II pneumocytes, Clara cells and basal cells of the bronchiole. SP-A and KL-6-positive cuboidal cells are more prominent in the less fibrous areas with grade 3 to 6, especially KL-6-positive cuboidal cells. These results are consistent with several reports on serum markers of an active phase of interstitial pneumonias with ongoing epithelial and capillary damage.

Type II pneumocytes and regenerative epithelium also produce chemotactic factors for fibroblasts such as fibronectin and TGFβ and PDGF. It has been demonstrated that TGFβ is ubiquitously expressed in pulmonary epithelial cells in normal and fibrotic lungs. In this study, TGFβ was expressed mainly in the regenerative cuboidal cells and flattened cells in the areas than in non-ciliated columnar cells, indicating that these cells appear in the sites of active fibroblastic proliferation in UIP and NSIP. The TGFβ family has been implicated in the fibrosis in interstitial lung disorders. TGFβ family is a chemoattractant for fibroblasts, so that at sites of injury the presence of TGFβ could expand the population of fibroblasts, which are the main source of connective tissue proteins. Our results suggest that TGFβ in regenerative epithelium may participate in a more active fibroblastic proliferation process.

In conclusion, regenerative epithelial cells in remodeling area in UIP may be derived from bronchiolar basal cells and Clara cells, while most of those in NSIP may be derived from type II pneumocytes. The different origin of regenerative epithelium may reflect the severity and extent of the injury and the degree of consequent fibrosis in UIP and NSIP.

References


