A Study of Oral Irritation Fibroma with Special Reference to Clinicopathological and Immunohistochemical Features of Stromal Spindle Cells

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Abstract

Background. Oral irritation fibromas (OIFs) are benign fibroblastic proliferations arising from the oral mucosa in response to chronic irritation. Although the nature of fibroblast proliferation has been well studied in wound repair, details of the histopathogenesis of spindle cells in relation to their immunohistochemical features and distribution in OIF are unclear. Methods. Forty cases of OIF were investigated and the spindle cells were examined in detail. The stromas were classified histopathologically, and stained histochemically by the alcian blue (pH 2.5)-PAS double-staining method. Immunohistochemistry was performed using antibodies against vimentin, α-smooth muscle actin (α-SMA), desmin, S-100β, myoD1, and collagen type I and III. Results. Histopathologically, the stromas of OIFs were classified into five types: mature, immature fibroblastic, immature inflammatory, myxoid and mixed type. Inflammation was only seen in a minority of cases with no mitotic figures or any sign of necrosis. Histochemically, the myxoid type stained basophilic while the collagen of other OIF types stained acidophilic. Immunohistochemically, the spindle cells of the mature type expressed vimentin constantly (V phenotype). In contrast, the spindle cells of the immature fibroblastic type expressed α-SMA (VA phenotype) and the immature inflammatory type expressed desmin (VD phenotype). Interestingly, the spindle cells of the myxoid type expressed S-100β (N phenotype), while the mixed type exhibited α-SMA and S-100β positive cells (VA/N phenotype). MyoD1 was expressed constantly in spindle cells of the immature inflammatory and fibroblastic types, but its expression was weak in the mixed type. MyoD1 was not expressed in the mature or myxoid types. All 40 cases stained positive for collagen type III, while collagen type I was detected predominantly in the mature type and only weakly in the other types. Conclusion. These results suggest that spindle cells of OIFs transiently express myofibroblastic characteristics, particular the VA, VD and VA/N phenotypes, through the expression of α-SMA, desmin and myoD1. Thus, with the onset of trauma (weak or chronic irritation) a myofibroblastic stromal reaction appears to be evoked in undifferentiated mesenchymal cells, and collagen type III is produced. As the healing process proceeds, collagen type III levels decline, collagen type I is secreted and the phenotypic features of myofibroblasts disappear, as seen in the V phenotype. The myxoid type expressed immunohistochemical features of neural differentiation while the mixed type expressed features considered to be of dual origin. The immunohistochemical findings also revealed that the growth of OIF was time-dependent.

Keywords:
Oral irritation fibroma, spindle cells, fibroblasts, myofibroblasts, clinico-pathology, immunohistochemistry
**Introduction**

Oral irritation fibromas (OIFs), or traumatic fibromas, are a benign reactive tumor of fibrous connective tissue formed in response to local irritation or trauma (1). Some studies have reported a female predilection, and while tumors can appear at any age, most biopsies are performed between the fourth and sixth decades of life (2, 3). Recurrence is unlikely unless the inciting trauma continues or is repeated. Within the mouth, the most common sites for OIFs are the buccal and labial gingiva and the lateral surface of the tongue (4).

Histopathologically, OIFs are characterized by their dome shape with a keratinized stratified squamous epithelium, dense bundles of collagen fibers, spindle- or fibroblast-like cells, relatively few blood vessels and inflammatory cells in the submucosa (5). Although OIFs have been widely studied, the immunohistochemical phenotypes of the spindle cells have not been fully investigated. The identification of cytoskeletal differentiation markers in spindle cells has recently led to the recognition of a phenotypic heterogeneity among these cells. Thus, spindle cells have been found to express morphological and biochemical features of myofibroblasts under physiological conditions as well as in the pathological settings (6). Pathologically, the phenotypes of spindle cells were characterized by α-SMA and desmin expression during wound healing and in tissues undergoing fibrosis, and these cells were thought to be the cause of the increased contractility of the affected tissues (7, 8).

Histopathological and immunohistochemical studies have been performed on benign fibrous tumors, hypertrophic scars, epithelial hyperplastic lesions and squamous cell carcinomas of the larynx, but there have been no detailed studies of OIF (9, 10). Therefore, the aim of this study was to investigate the clinicopathological, histochemical and immunohistochemical characteristics of OIF and related stromal spindle cells. Also, the immunohistochemical findings, which indicate myofibroblast differentiation in OIF, are discussed.

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**Materials and Methods**

**Subjects**

The study comprised 40 cases of OIF diagnosed histopathologically between 1971 and 2003 in the Department of Oral Pathology, Nihon University School of Dentistry at Matsudo, Japan. All patients gave written informed consent to participate in the study (Recognition number of the committee: EC-04-008). All patients were ≥29 years of age. The surgical reports were assessed for tumor location, duration and size. The resected specimens had been immediately fixed in 10% neutral formalin solution and paraffin embedded blocks had then been prepared according to the standard method. Serial sections (4 μm thick) were prepared from the paraffin blocks for histopathological, histochemical and immunohistochemical observation.

**Light microscopy and histochemical staining**

Sections were stained with hematoxylin-eosin (HE) and alcian blue (pH−2.5)–PAS double-staining. All 40 cases were classified on the basis of their histological appearance in sections stained with HE.

**Immunohistochemical staining**

Sections were deparaffinized in xylene and dehydrated in Tris-buffered saline (TBS, Takara, Japan, Code No. T903 in 0.05 M sodium citrate, pH−7.6). For antigen detection, the envision+ labeled streptavidin-biotin (LSAB 2 kit, Dako A/S, Canada) technique was used. Primary antibodies, directed against the following antigens, were used at the dilutions indicated: α−smooth muscle actin (1A4, α-SMA, 1: 50; Dako Cytomation, Canada), desmin (D33, 1: 50; Dako Cytomation, Canada), S−100β (2A10, 1: 200; Biological Laboratories, Japan), collagen type 1 and III (1−8H5, III−53, 1: 50; Daiichifain Chemical, Japan), vimentin (Vim 3B4, 1: 50; Dako Cytomation, Canada) and myoD1 (5.8A, 1: 50; Dako Cytomation, Canada). The Dako Catalysed Amelamation System (CSA, DAKO A/S, Denmark) was used as a primary antibody against myoD1. Sections were incubated with antibody at the indicated dilution for 60 min at room temperature according to the manu-
facturer’s instructions, except in the case of myoD1, where incubation was carried out for 15 min. To improve detection, deparaffinized sections were pretreated by microwave heating. Peroxidase activity was visualized using diaminobenzidine. Finally, all sections were counterstained with Mayer’s hematoxylin.

Based on immunohistochemical findings, OIFs were grouped according to the spindle cell phenotype and criteria of Schurch et al. (11): V phenotype—only vimentin detected; VA phenotype—vimentin and \( \alpha \)-SMA; VD phenotype—vimentin and desmin. For the N phenotype: vimentin and S-100\( \beta \), and VA/N phenotype: vimentin, \( \alpha \)-SMA and S-100\( \beta \), the authors named the phenotypes based on cytoskeletal characteristics.

For negative controls, primary antibodies were omitted. Positive controls consisted of specimens of normal gingiva for collagen type I and III, rhabdomyosarcoma for myoD1, leiomyoma for \( \alpha \)-SMA, and schwannoma for vimentin, desmin and S-100\( \beta \).

**Results**

**Clinicopathological findings**

The clinical data for the 40 cases are summarized in Table 1. The patients ranged in age from 29–90 years (mean 50.0±14.1 years), with the majority between 50 and 60 years of age. The duration of OIFs ranged from 1 month to over 6 years, and the diameter of the tumors ranged from 0.4–3.4 cm (mean 2.0±1.1 cm). Generally, the longer the duration of the OIF, the smaller its diameter. Overall, most OIFs were found on the cheek and gingiva.

**Histopathological findings**

The histopathological data for the 40 cases of OIF is summarized in Table 2. Microscopically, the OIFs appeared as a nodular mass of fibrous connective tissue covered with stratified squamous epithelium. The connective tissue was either dense or less collagenized. All tumors were composed of spindle-shaped cells, with the cells varying from slender to plump and resembling fibroblasts set in a collagenous or fibromyxoid stroma. Inflammation was only seen in a minority of cases with no mitotic figures or any sign of necrosis. The OIFs were divided into five stromal types based on microscopic appearance: mature (n=19), immature fibroblastic (n=7), immature inflammatory (n=3), myxoid (n=7) and mixed (n=4). The mature type, consisting mainly of dense collagenous stroma with a few to moderate number of spindle cells, was the most common (Fig. 1). The duration of this type was more than 6 years and the size of the tumors ranged from 0.5–2.4 cm (mean 1.2 cm). The immature fibroblastic type comprised loosely collagenous stroma with highly cellular areas of spindle cells, and the inflammatory type consisted of scattered inflammatory cells with slight to moderate vascular proliferations (Figs. 2-a and 3-a). The duration and size of these two types were almost similar: less than 3 years duration for both types, and 1.2–3.5 cm (mean 2.2 cm) in size for the immature fibroblastic and 1.0–3.5 cm (mean 2.4 cm) for the immature inflammatory type. The myxoid type was composed mainly of prominent loose myxoid stroma while the mixed type consisted of both myxoid and immature fibroblastic stroma (Figs. 4-a and 5-a). Again the duration and size of these two types were almost similar: less than 2 years duration and 1.3–2.5 cm (mean 2.0 cm) in size for the myxoid type and 1.4–2.9 cm (mean 2.1 cm) for the mixed type.

Histochemically, using the alcian blue (pH 2.5)-
Table 2. Clinicopathological and immunohistochemical findings.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Immunohistochemical phenotype</th>
<th>No. (%)</th>
<th>α-SMA</th>
<th>Desmin</th>
<th>Vimentin</th>
<th>S-100β</th>
<th>Collagen type I</th>
<th>Collagen type III</th>
<th>MyoD1</th>
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<tbody>
<tr>
<td>Mature</td>
<td>V</td>
<td>19 (47.5)</td>
<td>−</td>
<td>−</td>
<td>++</td>
<td>−</td>
<td>++</td>
<td>++</td>
<td>−</td>
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<td>&gt; 6 yrs &amp; 0.5-2.4 cm (1.2 cm)</td>
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<tr>
<td>Immature</td>
<td>VA</td>
<td>7 (17.5)</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>−</td>
<td>−~+</td>
<td>++</td>
<td>+</td>
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<tr>
<td>fibroblastic</td>
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<td>&lt;3 yrs &amp; 1.2-3.5 cm (2.2 cm)</td>
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<tr>
<td>Immature</td>
<td>VD</td>
<td>3 (7.5)</td>
<td>−</td>
<td>+</td>
<td>++</td>
<td>−</td>
<td>−~+</td>
<td>++</td>
<td>+</td>
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<td>inflammatory</td>
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<td>&lt;3 yrs &amp; 1.0-3.5 cm (2.4 cm)</td>
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<tr>
<td>Myxoid</td>
<td>N</td>
<td>7 (17.5)</td>
<td>−</td>
<td>−</td>
<td>++</td>
<td>++</td>
<td>±~+</td>
<td>++</td>
<td>−</td>
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<td>&lt;2 yrs &amp; 1.3-2.5 cm (2.0 cm)</td>
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<tr>
<td>Mixed</td>
<td>VA/N</td>
<td>4 (10.0)</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>+</td>
<td>~+</td>
<td>++</td>
<td>−~+</td>
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<tr>
<td>&lt;2 yrs &amp; 1.4-2.9 cm (2.1 cm)</td>
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* : Spindle cell phenotypes: typing is according to Schurch. W. et al. (Histology for pathologists, 2nd, Raven, New York 1999, 129-65
** : Expressions of spindle cells
*** : Spindle cells expression considered of neural origin

PAS double-staining method, the more collagenous types stained acidophilic with Schiff’s reagent and the myxoid type stained basophilic with alcian blue (Figs. 1b and 4b).

Immunohistochemical findings

The immunohistochemical results are also summarized in Table 2. Five phenotypes of spindle cells were identified based on their immunoreactivity for α-SMA, desmin and myoD1, and taking into account their general staining with vimentin antibody; those with V phenotype were positive for vimentin only (Fig. 1c), those with VA phenotype were positive for α-SMA (Fig. 2b), and those with VD phenotype were positive for desmin (Fig. 3b). The study also identified two other spindle cell characters and defined them as negative for α-SMA and positive for S-100β were considered N phenotype (Figs. 4c and d), while those positive for both α-SMA and S-100β were considered VA/N phenotype (Figs. 5b and c). Overall, the expression of vimentin, α-SMA, S-100β and desmin was chiefly observed in the cytoplasm of the spindle cells. MyoD1 was expressed on the spindle cell nuclei of immature fibroblastic and inflammatory types (Figs. 2c and 3c), but only weakly in the mixed type and not at all in the mature and myxoid types. Collagen type I was expressed in the matrix and the cytoplasm of spindle cells, mainly in the mature type (V phenotype; Fig. 1d) while collagen type III was generally expressed by all spindle cell types (Figs. 2d and 3d).

Immunohistochemical staining revealed that all 40 cases were vimentin-positive. Certain spindle cells within these cases expressed α-SMA, desmin and myoD1 (Figs. 2b and c, 3b and c, and 5b, arrowheads), and were considered myofibroblasts, based on previous findings (12-14). In the mature type, no markers of myofibroblasts were found in the V phenotype. In contrast, VA and VD phenotypes were present in immature fibroblastic and inflammatory types. Of the seven cases of myxoid type, all were N phenotype and positive for S-100β. Finally, the VA/N phenotype was present in the mixed type, with α-SMA and S-100β positive cells.
Fig. 1a. Low-power microscopic image of mature type showing a dome-shaped lesion consisting of mainly dense fibrous stroma with few to moderate numbers of stromal spindle cells. There is little or no inflammation (hematoxylin-eosin, original magnification ×100).

Fig. 1b. Mature type showing acidophilic stroma (alcian blue (pH 2.5)-PAS double staining method, original magnification ×200).

Fig. 1c. Mature type showing immunostained spindle cells (fibroblasts). These cells stain positive for vimentin (V phenotype) (original magnification ×200).

Fig. 1d. Mature type showing diffuse collagen staining. Collagen type I is present (V phenotype) (original magnification ×200).

Fig. 2a. Low-power microscopic image of immature fibroblastic type showing loosely fibrous stroma with many scattered spindle cells (hematoxylin-eosin, original magnification ×100).

Fig. 2b. Immature fibroblastic type showing α-SMA staining (VA phenotype). Cells are identified as myofibroblasts (arrowheads) (original magnification ×200).

Fig. 2c. Immature fibroblastic type showing myoD1 stained spindle cells. Cells are identified as myofibroblasts (arrowheads) (original magnification ×200).

Fig. 2d. Immature fibroblastic type showing diffuse collagen staining. Collagen type III is present (original magnification ×200).

Fig. 3a. Low-power microscopic image of immature inflammatory type showing loosely fibrous stroma with scattered inflammatory cells and vascular tissue (hematoxylin-eosin, original magnification ×100).

Fig. 3b. Immature inflammatory type showing positively desmin stained spindle cells. Cells are identified as myofibroblasts (arrowheads) (VD phenotype) (original magnification ×200).

Fig. 3c. Immature inflammatory type showing myoD1 stained spindle cells. Cells are identified as myofibroblasts (arrowheads) (original magnification ×200).

Fig. 3d. Immature inflammatory type showing diffuse immunostained collagen. Collagen type III is present (original magnification ×200).

Fig. 4a. Low-power microscopic image of myoid type showing loose myxoid stroma (hematoxylin-eosin, original magnification ×100).

Fig. 4b. Myxoid type showing acidophilic stroma (N phenotype) (alcian blue (pH 2.5)-PAS double staining method, original magnification ×200).

Fig. 4c. Myxoid type showing negative immunostaining for α-SMA (original magnification ×200).

Fig. 4d. Myxoid type showing spindle cells positive for S-100β (arrowheads) (N phenotype) (original magnification ×200).

Fig. 5a. Low-power microscopic image of mixed type showing both myxoid and immature fibroblastic stroma (hematoxylin-eosin, original magnification ×100).

Fig. 5b. Mixed type showing α-SMA positive myofibroblasts (arrowheads) (VA/N phenotype) (original magnification ×200).

Fig. 5c. Mixed type showing S-100β positive spindle cells (VA/N phenotype) (arrowheads) (original magnification ×200).

Discussion

OIF is believed to result from low intensity and prolonged chronic irritation such as biting, calculus and food impaction (1). Overall, 40 cases of OIF diagnosed at our hospital between 1971 and 2003 were selected for this study. The mean age of patients with OIF was 50 years, with lesions were observed most frequently on the cheeks (30%) and labial gingiva (20%). These results are in support of previous findings (3, 4).

Based on histological findings, the present study identified five stromal types of OIF with no mitotic figures or signs of necrosis. The mixed type identified in this study has not been described previously in the literature (1, 5). The mature type was most common in the present study, followed by the myxoid, immature fibroblastic, mixed and immature inflammatory types. Mighell et al. have previously reported that reactive overgrowths of oral mucosa have diverse histopathological appearances, but the composition of their connective tissue needed clarification (15). In the present study, the mature type consisted of dense collagenous tissue containing few to moderate numbers of spindle cells with no inflammation. The duration of the mature type of OIF was 6 years or longer and the lesion had a small diameter. These findings suggest that the mature type of OIF may reach a certain size and then become stable or gradually regress following removal of the irritation. The mature type of OIF corresponded to the V phenotype with no expression of α-SMA and desmin, suggesting the disappearance of myofibroblasts after healing, associated with an increased expression of collagen type I (16, 17). Seemayer et al. and others have reported similar findings, and have shown that, with time, a more rigid collagen type I appears concomitant with the disappearance of myofibroblasts (18, 19). Since no cases of mature type OIF (V phenotype) showed actin or desmin-positive spindle cells, it is presumed that this type consists mainly of
fibroblasts.

In contrast to the mature type, the fibroblastic type of OIF consisted of loose collagenous stroma with abundant spindle cells, while the immature inflammatory type was composed of scattered inflammatory cells and slight to moderate vascular proliferations. The associated inflammatory changes were most likely the response to irritation or trauma, and these changes may be required to produce the morphological changes in stromal spindle cells. These tumors were generally of lesser duration (a few months to less than 3 years) than mature type OIFs, and were larger in size. Based on these findings, it appears that these benign tumors may have grown more rapidly with greater initial production of granulation tissue followed by a slower growth over time. The immature fibroblastic and inflammatory types correspond to VA and VD phenotypes, respectively. These phenotypes are associated with expression of α-SMA and desmin, and thus the presence of myofibroblasts. The appearance of myofibroblasts and the associated increased expression of collagen type III shown in this study were features that occurred following induction of injury. It has been suggested that granulation tissue is initially characterized by collagen type III expression, possibly the product of myofibroblasts, which provides plasticity to the wound in the early stage of healing. These cells have been demonstrated to appear in response to injury and repair as mediators of contractile forces and elaborators of cellular products (17, 20).

Since myofibroblasts share morphological and functional features of fibroblasts and smooth muscle, it is reasonable to postulate that these stromal spindle cells were derived from either one or possibly more undifferentiated mesenchymal cells. The results of the present study also demonstrated that the stromal spindle cells of OIFs synthesize collagen type I and III, a characteristic of granulation tissue, therefore supporting the concept that myofibroblasts are derived from undifferentiated mesenchymal cells (7, 21). These findings might also explain the histopathogenesis and pattern of the early stages of OIF wound healing. Thus, any undifferentiated mesenchymal cells might transform transiently to myofibroblasts in response to chronic irritation, and this is supported by findings of the present study. Moreover, Gabbiani and Majno have described spindle-shaped cells with structural properties of myofibroblasts in Dupuytren’s disease as well in fibrous hamartoma of infancy (22). It has also been postulated that angiogenesis takes place in a coordinated manner and that granulation tissue acquires its typical features during this stage, as supported by the results of the present study (7).

The myxoid and mixed types of OIF had similar features, except that the latter had cellular as well as myxoid components. Clinicopathologically, the tumors were younger and were of shorter duration but larger size compared to mixed type. These two types corresponded to N and VA/N phenotypes and were defined by the authors according to the expression of S-100β in both and α-SMA in the latter, representing focal myofibroblastic differentiation. The significance of the S-100β immunoreactivity observed is uncertain although it is possible that neural differentiation occurs in the N phenotype, whereas a dual origin is considered in the VA/N phenotype. In addition, the expression of S-100β supports the results seen with neural tumors that these cells arose from neuroectodermal nerve sheath elements such as embryonal neuroectodermal cells (23).

MyoD1 antibody is a DNA-binding nuclear protein that initiates myogenesis in mesenchymal stem cells. This antigen is expressed weakly to strongly in immature fibroblastic/inflammatory and mixed types, corresponding to VA, VD and VA/N phenotypes. In this study, the authors also defined those cells expressing myoD1 as myofibroblasts. Their presence may play a role in cell differentiation and is essential for the repair and healing process (24). In addition, it has been suggested that stromal cells express vimentin. Some of these cells have been found to express actin, desmin and myoD1 also, suggesting that some of these stromal cells are equipped with muscular elements and might participate in wound contraction (6, 25, 26). It has been shown that myoD1 can stain the
nuclei of myoblasts and the nuclei of non-muscle tissue (27), as revealed in some cases in the present study.

Alcian blue (pH 2.5) - PAS double-staining revealed differences in between collagenous and myxoid components. The collagenous component was acidophilic with Schiff’s reagent in contrast to the myxoid component, which stained basophilic with alcian blue. It has been suggested that acid mucopolysaccharides in myxoid stroma are produced by spindle cells with a neurogenic origin (28, 29), while Ishikawa and others have suggested that the myxoid stroma could be a manifestation of a degenerative change (30, 31). It is also proposed that it is a combination of neurogenic and degenerative changes that results in the formation of the myxoid stroma (32, 33). However, further studies are necessary to clarify the origin and histogenesis of myxoid acid mucopolysaccharides.

Overall and highlighting the features of stromal spindle cells and the importance of myofibroblasts identified in these OIFs, it is interesting to speculate how the immunohistochemical appearances were derived. However, before these phenotypes can be identified, it is necessary to understand the clinicopathological features of OIFs, particularly their duration and size. Thus, the main clinicopathological features of OIFs were investigated and matched to the immunohistochemical findings. It is believed that myofibroblasts are among the OIF spindle cells that appear at discrete time points induced by irritation or trauma. In addition, based on their duration, size, and immunohistochemical findings, it is suggested that these cells derive from undifferentiated mesenchymal cells after appropriate stimulation. In fact, it has been shown that within each histological type, spindle cells have variable phenotypes, which are expressed in OIF stromal components. These cells have been shown to migrate into the wound and their active contraction decreases the wound defect (8). After healing, one can hypothesize that myofibroblasts transform into fibroblasts, as shown in the mature type, resulting in disappearance of myofibroblasts and an associated increase in extracellular material such as collagen type I (15). In addition, the myxoid and mixed types were accurately defined in this study, better reflecting their composition of spindle cells and myxoid background.

In conclusion, this study showed that myofibroblasts play an important role in OIF histopathogenesis in terms of the stromal response to irritation, injury and repair (13). Immunohistochemical analysis of OIFs provided useful information on the phenotypic character of OIF spindle cells, which is relevant for understanding their critical role in stromal tissue injury. Stromal spindle cells in OIF are relatively undifferentiated and could assume a particular phenotype depending on the microenvironmental stimuli.

Acknowledgments

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