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RESEARCH ARTICLE

MYOFIBROBLAST AND ITS ROLE IN ORAL LESIONS

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ABSTRACT

Myofibroblasts are modified fibroblasts with smooth muscle like features characterized by the presence of contractile apparatus. Myofibroblasts have an important position in the inflammatory response. They produce matrix molecules such as collagen, glycosamino-glycans, tenascin and fibronectin in the interstitial space or basement membrane and play important role in growth, differentiation and wound healing which if deranged or separated can result in tissue fibrosis. Myofibroblasts interact with epithelial cells and other connective tissue cells and may thus control such phenomena as tumour invasion and angiogenesis. Myofibroblasts also promote invasion by altering the composition of the tumour micro environment and are prognostic. Myofibroblasts in the stroma of OSCC may influence proliferation and invasion, resulting in more aggressive tumour. Myofibroblasts in the stroma of odontogenic lesions also play an important role in their aggressive biological behaviour. As they are present in virtually every tissue, it is possible that they may play a role in multisystem diseases. Understanding the role of the stromal cells and extracellular matrix will allow us to identify more precise prognostic markers and potentially device new therapeutic options and prevent various diseases caused by these miraculous multipotential cells.

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INTRODUCTION

Fibroblasts are ubiquitous mesenchymal cells that are normally found in the stroma of many tissues (Gartner and Hiatt, 2001). At the stage when they are actively producing intercellular substances, they either possess wide cytoplasmic processes or appear spindle shaped. Their abundant cytoplasm is markedly basophilic and their nucleoli are generally prominent, indicating active protein synthesis (Ham, *et al.,* 1987). Their nuclei are relatively large, active or euchromatic (open faced) and possess prominent nucleoli. In young and active cells the cytoplasm is abundant and basophilic because of the high concentration of rough endoplasmic reticulum. The same cells become less active during adult life and are then often referred to as fibrocytes (Ham, *et al.,* 1987).

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After tissue injury, fibroblasts differentiate into contractile and secretory myofibroblasts that contribute to tissue repair during wound healing (Hinz *et al.,* 2007). Myofibroblasts are modified fibroblasts that demonstrate characteristics similar to those of both fibroblasts and smooth muscle cells. Fibroblasts and myofibroblasts are not easily distinguished by routine light microscopy (Gartner and Hiatt, 2001). The myofibroblast has been initially identified by means of electron microscopy in granulation tissue of healing wounds as a modulated fibroblast exhibiting features of smooth muscle (SM) cells, such as bundles of microfilaments, with dense bodies scattered in between and gap junctions (Gabbiani, 2004). Myofibroblasts are present in organs with a high remodelling capacity such as kidneys, lungs and the periodontal ligament or during increased remodelling, such as in growth, development, inflammatory responses and the contraction of healing wounds. Myofibroblasts cause the extracellular matrix to contract and are occupied in the regulation of proliferation and differentiation of neurogenic, vascular and epithelial cells

(Shirol and Shirol, 2012). Myofibroblasts may be defined morphologically and immunologically through identification of expressed cytoskeletal proteins. The simplest definition of a myofibroblast is that they are smooth-muscle-like fibroblasts. Some investigators choose to call them smooth-muscle-like cells or activated smooth muscle cells. It may well represent an intermediate state between fibroblasts and smooth muscle cells (Powell *et al.,* 1999).

MORPHOLOGY

Myofibroblasts have several unique morphological characteristics, few of which are present in fibroblasts as well as smooth muscle cells. They exhibit distinct cytoplasmic actin microfilaments (stress fibers) and they are connected to each other by adherens and gap junctions. These cells are also in contact with extracellular matrix - ECM by focal contacts known as fibronexus, a transmembrane complex made up of intracellular contractile microfilaments and the ECM protein fibronectin. Transmission electron micrograph shows, the cell membrane displays numerous caveolae. The actin microfilament bundles are distinct. The cytoplasm is rich in rough endoplasmic reticulum - RER, Golgi apparatus and mitochondria. Nucleus of an activated myofibroblasts shows multiple indentations. Adherens and gap junctions are present between myofibroblasts (Powell *et al.,* 1999). Phase-contrast micrographs (A and B) and scanning electron micrographs (C and D) of stellate cells.

The stellate myofibroblast displays a highly refractile cell body on phase contrast microscopy and possesses a highly arborized array of cell processes with several orders of bifurcation. The cell processes are devoid of microvilli, whereas the cell body shows a dense array of long microvilli, giving it a shaggy appearance.

Functions

There are several common normal activities of myofibroblasts. First, through mesenchymal- epithelial interactions, myofibroblasts are key components of organogenesis or morphogenesis, i.e., the growth and differentiation of the tissue or organ. They do so through the secretion of soluble mediators of inflammation and growth factors and expression of their receptors and through secretion and formation of interstitial matrix and/or basement membrane molecules. Myofibroblast also play a fundamental role in many disease states, either through activation and proliferation or through deletion. They play a central role in wound healing, presumably as an extension or accentuation of their role in normal growth and differentiation. They appear to be involved in the formation and repair of the extracellular matrix (ECM) and proliferation and differentiation of epithelial (or parenchymal), vascular and neurogenic elements (Powell *et al.,* 1999). Myofibroblasts play a major role in the inflammatory response.

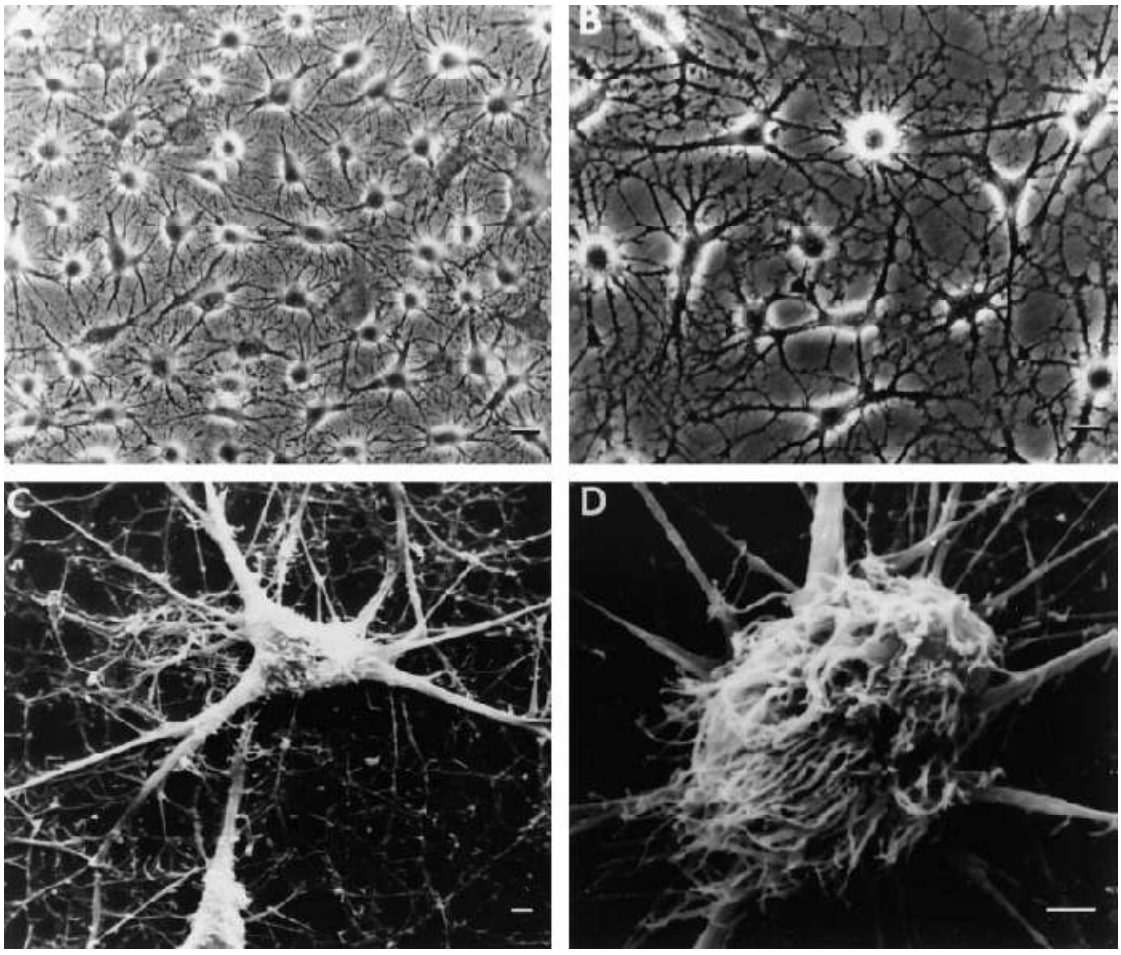

Figure 1. Phase-contrast micrographs (A and B) and scanning electron micrographs (C and D) of stellate cells

These cells are avid producers of both chemokines and cytokines and are capable of augmenting or down regulating the inflammatory response by the secretion of these soluble mediators of inflammation. They also synthesize prostaglandins, expressing both the constitutive cyclooxygenase-1 (COX-1 or PHS-1) gene product and the inducible COX-2 (PHS-2) protein (Hull *et al.,* 1995). Myofibroblasts also express α and β integrins that are part of the adhesion mechanism of myofibroblasts to matrix proteins. Through these or other properties, myofibroblasts participate in the formation of tissue granulomas. Granulomas themselves are impressive factories of cytokines and other inflammatory mediators. Last, production of matrix molecules such as collagen, glycosaminoglycans, tenascin, and fibronectin in the interstitial space or basement membrane is part of the structure, growth, differentiation, and wound healing function of myofibroblasts. These processes, when unchecked, deranged, or repeated, can result in tissue fibrosis. Therefore, fibrotic disease is a major pathological end point of activated and proliferating myofibroblasts in most, if not all, tissues (Greenhalgh *et al.,* 1990).

- Actin, a component of the microfilaments
- Vimentin, desmin, lamin, or glial fibrillary acidic protein (GFAP), members of the intermediate filament system and
- The tubulins of the microtubules.

Based on immunohistochemical staining of these filaments in a given tissue, a classification system has been proposed. Myofibroblasts that express only vimentin are termed V-type myofibroblasts, Those that express vimentin and desmin are called VD-type, Those that express vimentin, a-SM actin, and desmin are called VAD-type, Those that express vimentin and a-SM actin are called VA type and Those that express vimentin and myosin are called VM-type (Joyce *et al.,* 1987).

Origin and differentiation of Myofibroblasts

It is uncertain that the origin of Myofibroblasts is from progenitor stem cells (possibly neuroepithelial stem cells), from the neural crest or simply transdifferentiate from resident tissue fibroblasts or from tissue smooth muscle cells.

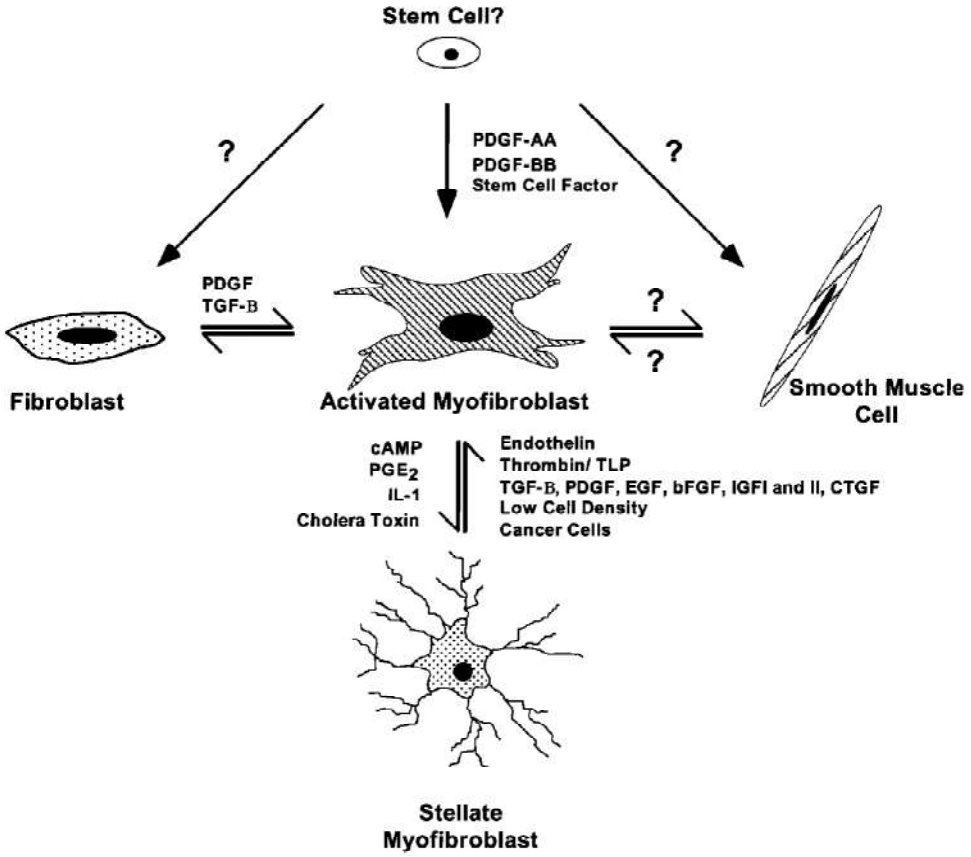

Figure 2. Proposed scheme depicting the origin, transdifferentiation, activation, and stellate transformation of myofibroblasts
PDGF, platelet-derived growth factor; TLP, tethered ligand protein; TGF-b, transforming growth factor-b; IL-1, interleukin-1; EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; IGFI, insulin-like growth factor I; CTGF, connective tissue growth factor.

Immunohistochemical features

Immunohistochemical characterization of myofibroblasts is based on antibody reactions to two of the three filament systems of eukaryotic cells.

These three systems are composed of:

Proto- myofibroblast differentiation from fibroblasts and subsequently into mature Myofibroblasts. Mechanical tension generated by migrating fibroblasts promotes the assembly of stress fibres characteristic of proto- myofibroblasts. The increasing number of fibroblasts in the wound area secretes new collagen and fibronectin. The orientation of the cells and fibres within this matrix is along the lines of tension and in line

to the wound surface. Small tractional forces that are exerted by the fibroblasts on recently formed matrix reinforce cell-matrix contacts, develop intracellular contractile stress fibres and hence become proto- myofibroblasts (Powell *et al.,* 1999). Platelet-derived growth factor (PDGF) plays an important role in this step of fibroblast differentiation into proto-myofibroblasts. Mechanical tension, transforming growth factor-TGFβ1 and ED-A FN (a variant of fibronectin) are key players in the differentiation of proto- myofibroblasts into mature myofibroblasts. Two soluble factors have been shown to promote differentiation from embryonic stem cells: PDGF and SCF (Anand-Apte *et al.,* 1997).

Proposed scheme depicting the origin, transdifferentiation, activation, and stellate transformation of myofibroblasts. PDGF, platelet-derived growth factor; TLP, tethered ligand protein; TGF-b, transforming growth factor-b; IL-1, interleukin-1; EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; IGFI, insulin-like growth factor I; CTGF, connective tissue growth factor.

Mechanism of myofibroblast origin

In case of wound healing and fibrotic diseases, dedifferentiation of epithelial cells by a process known as epithelial-mesenchymal transition (EMT), as well as, bone marrow- and tissue derived mesenchymal stem cells like fibrocytes can transform in to myofibroblasts (Mc Anulty, 2007).

remodelling, and gain a mesenchymal phenotype (Yanjia and Xinchun, 2007).

Different types of EMT

Type 1 EMT is associated with gastrulation and generation of mesoderm, endoderm, and neural crest. The primitive epithelium gives rise to primary mesenchyme through an EMT. Type 2 EMT begins as part of tissue repair to generate fibroblasts. Type 2 EMT can contribute to organ destruction if it is persistent if inflammation insult is not attenuated. Type 3 EMT occurs in epithelial cancer cells and affects oncogenes and tumor suppressor genes which conspire with the EMT proteome to result in increased invasiveness and migration.

Endothelial – Mesenchymal transition

Endothelial cells may act as a source of alpha-SMA expressing mesenchymal cells in lungs during fibrosis and it has been shown in the study of development of the vasculature and when they are stimulated with TGF-beta1 *in vitro* (Frid *et al.,* 2002).

Tissue derived Mesenchymal stem cells

Several studies have shown that mesenchymal stem cells reside within the tissues which are also known to be localised near vessel walls. Previous studies in the lung have suggested that following injury myofibroblasts may originate from perivascular and peribronchial sources (Mc Anulty, 2007).

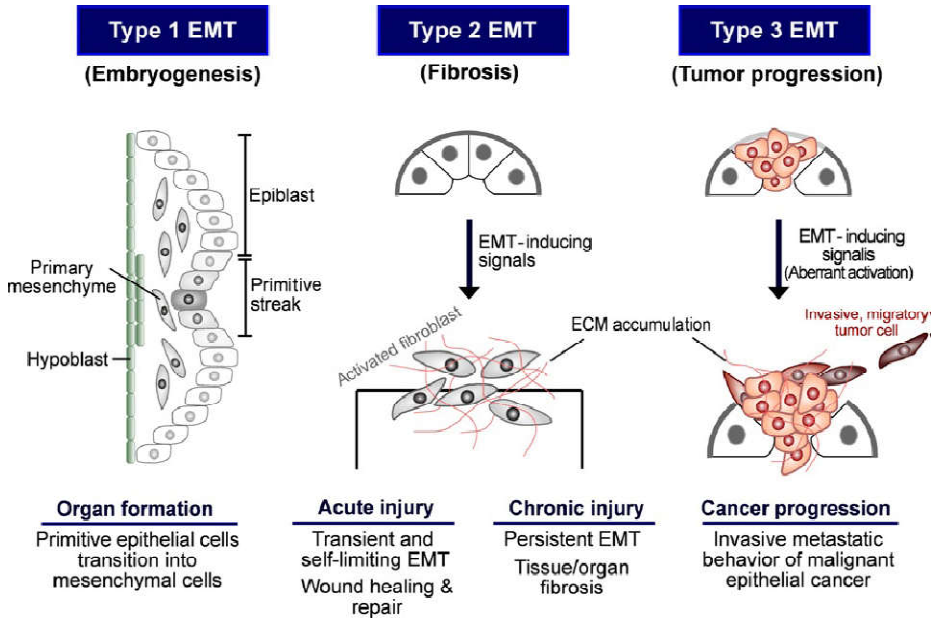

Figure 3. Different types of EMT

Epithelial- mesenchymal transition

Derivation of myofibroblasts from epithelial cells via EMT has been suggested recently by both *in vitro* and *in vivo* studies (Willis *et al.,* 2005). Epithelial–mesenchymal transition (EMT) is a process by which epithelial cells lose cell–cell attachment, polarity and epithelial specific markers, undergo cytoskeletal

Main myofibroblast progenitor after injury of different tissues seems to be the locally residing fibroblast, which transiently differentiates into a protomyofibroblast (Willis *et al.,* 2005), The local residing smooth muscle cells undergo de-differentiation by losing their smooth muscle markers to form differentiated myofibroblasts during atheromatous plaque formation (Willis *et al.,* 2005).

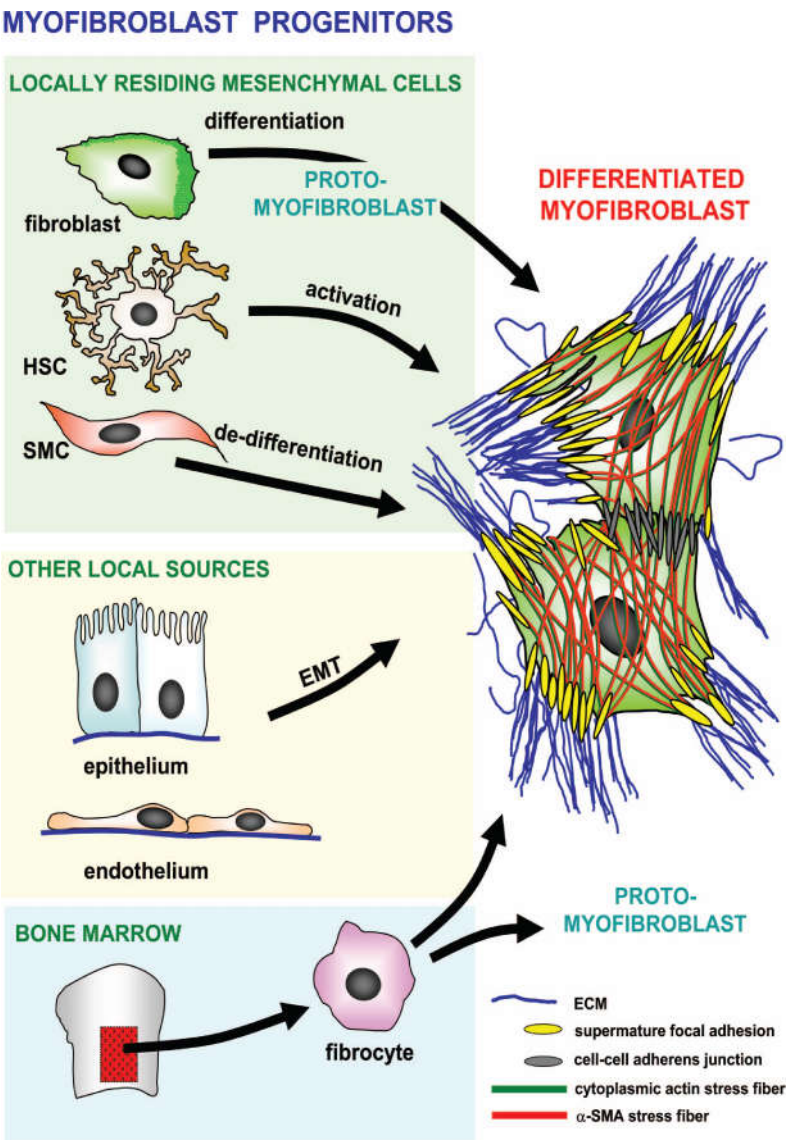

Figure 4. One cell, multiple origins

Bone marrow derived myofibroblasts

Myofibroblasts and fibroblasts and the extracellular matrix proteins they produce are key components of the desmoplastic response to tumors. Both myofibroblasts and fibroblasts can be bone marrow-derived, and this phenomenon is augmented by injury. Bone marrow contributes to tumor stroma. In the development of tumors, the interaction between the tumor and the host is often characterized by a desmoplastic reaction. The role of the desmoplastic response to tumors is not completely understood although a cancer-induced change in the stroma may contribute to cancer invasion. In normal circumstances, the interaction between normal epithelium and normal stroma helps to maintain tissue integrity. However, in cancer, the interaction between cancer cells and the surrounding stroma via signals such as transforming growth factor _ and platelet-derived growth factor results in the formation of an abnormal stroma, the disruption of tissue integrity, and hence invasion and ultimately metastasis.

Potential key participants in the development of this stroma are circulating fibroblasts, and there is evidence that given the appropriate environment, modulation of fibroblast differentiation toward a myofibroblast phenotype can occur (Dirkezie and Dilke, 2004).

The formation of proto-myofibroblasts

One crucial signal for the formation of the contractile features of the proto-myofibroblast is mechanical tension. Fibroblasts populating the granulation tissue of a wound that has been mechanically stressed by splinting with a plastic frame form stress fibres and therefore, proto-myofibroblasts earlier than normally healing wounds. Conversely, release of tension in wound granulation tissue and in the granuloma pouch leads to a gradual loss of stress fibres (Valentich *et al.,* 1997). Similarly, in normal tissues, proto-myofibroblasts are always present where there is the need to generate mechanical tension. In addition to mechanical tension, platelet-derived growth

factor (PDGF) helps in the formation of the protomyofibroblast (Grotendorst and Rahmanie, 2004).

Formation of differentiated myofibroblasts

Once proto- myofibroblasts have developed in response to mechanical stress, they can be stimulated to develop into differentiated myofibroblasts. Differentiated myofibroblasts can be distinguished from proto-myofibroblasts by the *de novo* expression of α-SM actin and the increased expression of ED-A fibronectin, as well as increased assembly of stress fibres and focal adhesions that become more and more complex. Many experiments and clinical observations have shown that TGF-β1 has a key role in stimulating all of these characteristics of the differentiated myofibroblast both *in vitro* and *in vivo*. TGF-β1 in damaged tissue could be derived from platelets, white blood cells (particularly macrophages) or parenchymal cells. Autocrine production of TGF-β1 by fibroblasts is of great importance in preserving the fibrogenic activity once the inflammatory stimulus has ceased. Injured epithelial cells can also produce TGF-β1, and thereby contribute to paracrine fibroblast stimulation (Tomasek *et al.,* 2002).

Myofibroblasts in pathology

During study of diverse pathologic conditions in which myofibroblasts have been described, three fundamental processes were defined (Seemayer *et al.,* 1980).

- Diverse responses to injury and repair phenomena
- Quasineoplastic proliferative conditions
- Tumors of myofibroblasts
- The stromal response to certain forms of neoplasia

The first group relates to granulation tissue and diverse tissue responses, such as burn contractures, pulmonary sarcoidosis, interstitial lung fibrosis, localized and systemic scleroderma, atherosclerotic plaques, cirrhosis, sinus tracts and ischemic ulcer beds, to cite a few. The myofibroblasts in these conditions mostly disclose the VA, but few may also disclose VAD (vimentin, alpha – SMA, desmin). The second group embodies the fibromatoses and other soft tissue proliferations that mimic sarcomas, such as nodular and proliferative fasciitis, proliferative myositis, cutaneous fibrous histiocytoma (dermatofibroma), elastofibroma, and others. In these conditions, the proliferating cells disclose, in decreasing order, the VA, the VAD, the VD, and the VA(D)M cytoskeletal phenotypes. The third group involves certain benign and malignant lesions with myofibroblast differentiation which includes myofibromas, myofibromatosis and myofibrosarcoma (Seemayer *et al.,* 1980). The forth group concerns the stromal response to neoplasia. Many invasive and metastatic carcinomas, especially those characterized by hard consistency, retraction, and fixation to adjacent tissues, elicit a desmoplastic stromal reaction that is rich in myofibroblasts. The retraction ascribed to such carcinomas has been attributed to the contractile forces generated by stromal myofibroblasts. They tend to be most numerous within the young mesenchymal stroma, areas that correspond to early stromal invasion or, more consistently, at the peripheral invasive cellular front of the tumor (Seemayer *et al.,* 1980).

Role of myofibrolasts in oral lesions

Oral dysplasias and hyperkeratosis

Using immunohistochemical methods, Vered *et al.,* (2009) studied the design and distribution pattern of myofibroblasts. Scanty arrangement was observed in hyperplasia and dysplasia. However, network arrangement and spindle arrangement of squamous cell carcinoma was observed in 23% and 77% of cases, respectively. They too, confirmed the role of network arrangement in invasive tumor behavior and weak prognosis of oral cancer. They also studied the diffuse and focal patterns of TGFβ1 cells and explained the relationship between positive TGFβ1 cell arrangement and tumor invasive behavior. Kellermann *et al.,* (2007) used αSMA immunohistochemical staining to study cell distribution and pattern of dysplasia and squamous cell carcinoma. Negative staining presented in all dysplastic lesions (Seifi *et al.,* 2010).

Odontogenic cysts and tumors

In Vered et al study, they reported that myofibroblasts in stromal surrounding of cysts and odontogenic tumors using immunohistochemical staining. They reported that αSMA expression in the stroma of solid ameloblastoma and odontogenic keratocyst (parakeratinized type) was higher than dentigerous cyst and unicystic ameloblastoma and ameloblastic fibro odontoma. Role of myofibroblasts in cystic walls is still not clear. Many cyst walls have long been known to be under strain exerted by a positive hydrostatic pressure from fluid content. The myofibroblasts have been proposed to be responsible for tensile force generation and their presence has become a general feature of tissues which are under continuous mechanical remodeling. In those cysts, were fluid content exerts positive hydrostatic pressure; the ordered formation of myofibroblasts in the wall may represent a homeostatic response, possibly there by resist the expansion of the cyst. With regard to inner zone of alpha-SMA positive cells, the area immediately below the lining epithelium contains inflammatory cells and acts as organizing granulation tissue which recruits the myofibroblast cells. They concluded that αSMA expression of myofibroblasts was an index of invasive behavior of odontogenic lesions and it seems that target therapy can be beneficial as an auxiliary method for treatment of more invasive lesions (Vered *et al.,* 2005). Differentiation of fibroblasts into myofibroblasts under the influence of TGFβ1 cytokine secreted from cancerous cells can cause cancer progression through parakrin effects stimulating angiogenesis. At the same time, autokrin effects cause Ras gene mutation and produces pre-invasive signals. (Varayoud *et al.,* 2001) (Seifi *et al.,* 2010). They hypothesized "when more MFs are present in the stroma, a more aggressive behavior of the odontogenic cysts and tumors can be anticipated". Lombardi *et al.* confirmed the presence of MF in odontogenic cysts wall and suggested that they might be part of a homeostatic response to the distension caused by cyst enlargement. The presence of MF in the stroma of DC and OKC in our study

may be related to cystic expansion (Mashhadiabbas *et al.,* 2010).

Central giant cell granuloma (cgcg)

Vered *et al.* investigated the correlation between MF density in aggressive and nonaggressive central giant cell granuloma (CGCG) and found that MFs were an integral component of CGCG stromal cells, but aggressive and nonaggressive lesions could not distinguished through the density of such cells (Vered *et al.,* 2007).

Mucoepidermoid carcinoma

One research described that stromal MF in low grade mucoepidermoid carcinoma (MEC) was higher than that in intermediate and high grades (MEC). They suggest that inflammatory infiltrate in the MEC stroma stop MF differentiation, being indicative of a worse prognosis, as it facilitates progression of neoplastic cells. Also, in their study the degree of myofibroblast proliferation was inversely related to the density of lymphocytic infiltration (Mashhadiabbas *et al.,* 2010).

Salivary gland tumors

Myofibroblasts were found at the tumor border in the majority of benign tumors, with a markedly decreased number in malignant tumors. The increased number of these stromal cells in benign lesions, with lesser involvement of malignant tumors, supports the role of myofibroblasts in tumor containment. The lack of myofibroblasts contributes to the ability of a malignant tumor to proliferate and spread. As with CD34-positive dendritic cells, there may be an epithelial-stromal relationship in which malignant epithelial cells secrete inhibitory factors, decreasing the numbers of myofibroblasts able to contain the malignant growth and spread. Myofibroblasts express different proteins, depending on the process in which they are involved, as well as the timing of the process.

For example, in granulation tissue, the myofibroblasts continuously express only vimentin, and ASMA expression is transient. A study by Dimanche-Boitrel et al showed that tumor-associated myofibroblasts from a rat colon-cancer cell line secreted a collagenase that could play a role in tumor invasiveness. In contrast, a study by Ooi et al revealed that ASMA-positive ‘‘myofibroblastlike’’ cells in the liver are associated with collagen formation. These studies suggest that myofibroblasts not only express different proteins depending on the biologic process, but display phenotypic and physiologic differences depending on the organ environment. They found that the ASMA-positive myofibroblasts were located in the inner layer of collagenous bundles at the tumor periphery, whereas DICs were present in the outer layers intimately associated with the myofibroblasts. These findings were similar to those published by Nakayama et al, who studied these same antigens in salivary gland pleomorphic adenomas. The presence of DICs in the outer layers of the tumor capsule may suggest a role of these cells in tumor growth by forming a myofibroblastic layer, which in turn gives rise to collagen production, a possible attempt at containing the tumor. However, owing to limited followup, these findings could not be correlated with the clinical outcome (Soma *et al.,* 2001).

Myofibroblasts in stromal response to carcinomas

Role of myofibroblasts on tumour stroma

Myofibroblasts modulate the stroma in physiology and pathology through direct cell–cell contacts and through secretion of matrix metalloproteinase (MMP)’s, tissue inhibitors of metalloproteinase (TIMP)’s, extracellular matrix (ECM) components, growth factors, cytokines, chemokines, and lipid products and through the expression of specific receptors (Wever *et al.,* 2008). Due to its ability to modify the extracellular matrix, myofibroblasts actively participate in tumor invasion and metastasis. Metastasis is a complex process that depends on many interactions among tumor cells and the microenvironment, involving a sequence of events characterized by tumor growth and angiogenesis, detachment between the tumor cells, invasion of the extracellular matrix (ECM), vascular dissemination, extravasation in target organs, and establishment of secondary tumor. During the ECM invasion, the tumor cell must adhere to its components, promote its degradation by metalloproteinases, and then move through the degraded ECM. This dynamic process of ECM remodeling, called stromagenesis, is orchestrated by stromal myofibroblasts and creates a permissive environment (Eliene-Magda *et al.,* 2012). Myofibroblasts do participate at numerous noncancerous pathological and physiological processes. During wound healing they assist at migration, proliferation, and contraction. When the wound is closed, myofibroblasts undergo apoptosis, quite in contrast to tumors where they persist as in a wound that does not close. This idea illustrates that cancer cells operate by noncancer specific activities, but they fail to regulate these activities properly. Myofibroblasts produce numerous molecules, growth and motility factors, angiogenic factors, extracellular matrix components, and proteinases, that all promote the invasion and also the growth of cancer cells. Other molecules of putative interest for invasion expressed by myofibroblasts include α-smooth muscle actin, vimentin, c-MET, proteolytic FAP displaying also dipeptidyl peptidase activity, cyclooxygenases (COX)-1 and -2 and N-cadherin, associated with β-catenin, β-catenin, p120CTN, and catenin (Mareel, *et al.,* 2003).

Conclusion

Great numbers of studies have been done on myofibroblasts in recent years. Advancement in diagnostic techniques has permitted accurate identification of this enigmatic cell. Controversies still continue regarding its origin. Broad spectrum of activities of myofibroblasts in diverse group of conditions ranging from wound healing to benign proliferations to malignancies has drawn the attention of multiple disciplines towards this cell. It is clear that our understanding of the myofibroblast, its origins, functions and molecular regulation will have a profound influence on the future effectiveness not only of tissue engineering but also of regenerative medicine generally (Tomasek *et al.,* 2002).

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