Review Article

Myofibroblasts: Master of disguise

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Abstract

Myofibroblasts are the unique population of smooth muscle-like fibroblasts. These cells have a role in growth factors secretion, matrix deposition and degradation. Thereby, myofibroblast contributes in both human physiology and pathology. This review explains the myofibroblastic lesions, imperative role of myofibroblasts in organogenesis, repair, regeneration, inflammation and tumorigenesis.

Keywords: Myofibroblasts, oral submucous fibrosis, squamous cell carcinoma, transforming growth factor-β, α-smooth muscle actin

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INTRODUCTION

Myofibroblasts are the modified fibroblasts armed with myosin and smooth muscle actin (SMA) and exert contractile force to condense the size of the wound.[1] Myofibroblasts are essential for the veracity of the mammalian body by virtue of their role in inflammation and repair, but can also become a threat by their ability to prop up tumor development.[2]

Giuho Gabbiani and Hartroft observed varying morphology of fibroblasts-like cells having cytoplasm loaded with filamentous structures 40–80 A° in diameter, a feature typical of smooth-muscle cells. Thus, hypothesized that these filament laden cells are responsible for wound contraction. This special cell received a name: "The Myofibroblast" in 1971.[3]

Origin of myofibroblasts

Myofibroblast can origin from various cells such as local fibroblasts, pericytes, smooth muscle cells, epithelial cells, endothelial cells, hepatic perisinusoidal cells, mesenchymal stem cells and fibrocytes [Figure 1].[2,4]

Formation of myofibroblasts

Endothelin-1 stimulates the proliferation and differentiation of fibrocytes to alpha SMA (α-SMA)-positive myofibroblast [Figure 2]. The contribution of bone marrow-derived stem cells to myofibroblast ranges from a few percent to approximately 80%.[5] Myofibroblasts are formed from epithelial cells by epithelial–mesenchymal transition.[6] Mesenchymal stem cells inhabiting in tissues, particularly those localized to vessel walls have a role in myofibroblast origin. These cells express α-SMA, a marker associated with myofibroblasts and smooth muscle cells.[6]

Formation of myofibroblasts from fibroblasts involves 2 steps [Figure 2][5]

- Formation of protomyofibroblasts

Under the mechanical tension, platelet-derived growth factor (PDGF) and stem cell factor (SCF), fibroblasts acquire stress

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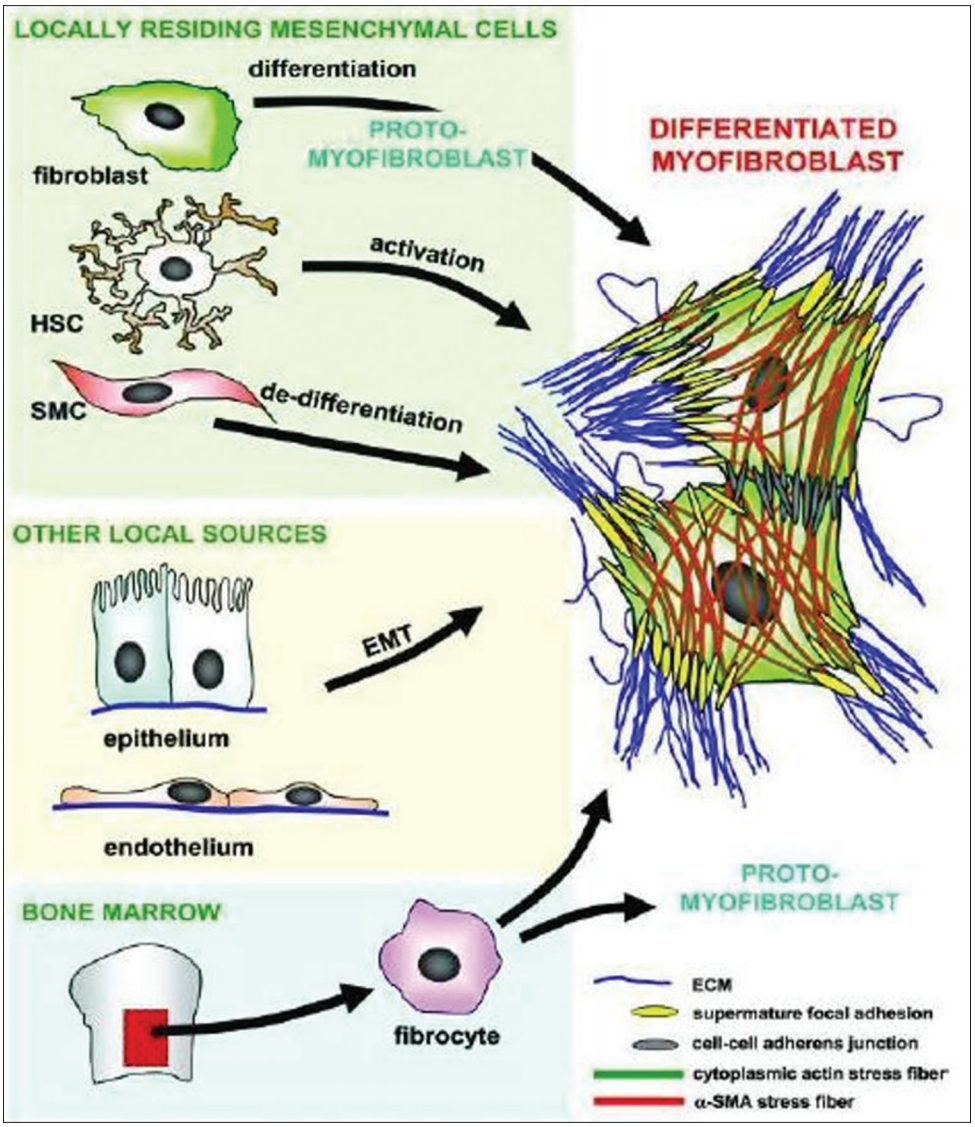

Figure 1: Progenitors of myofibroblasts

fibers, focal adhesion and become proto-myofibroblasts. However does not result in the formation of differentiated α-SMA positive myofibroblasts.[7]

- Formation of myofibroblasts

Accumulation of transforming growth factor-beta (TGF-β), the presence of specialized extracellular cellular matrix (ECM) proteins such as the extra domain A (ED-A) splice variant of fibronectin, high extracellular stress arising from the mechanical properties of the ECM and cell remodeling activity, mast cells derivates-histamine, tryptase and tumor necrosis factor- alpha (TNF α) are found to regulated the differentiation.[8]

Activation, proliferation and migration of myofibroblasts

Fibrogenic cytokines such as interleukine-1 (IL-1), IL-6, IL-8, TNF-α, PDGF, fibroblast growth factor (FGF) and TGF-β, aldosterone, thrombin and endothelin are responsible for activation and proliferation.[9] Myofibroblast activation requires the presence of matrix molecules, specifically ED-A domain of fibronectin. This fibronectin ED-A domain is necessary for TGF-ß to trigger α-SMA expression and secretion of collagen by myofibroblasts. Following the activation of myofibroblast, connective tissue growth factor (CTGF), TNF-α, IL-1, IL-6, IL-8, TGF-ß, EGF, FGF, IGF-I and IGF-II promote myofibroblast proliferation.[2,10]

Distribution

In oral cavity, myofibroblasts are found in gingiva, palatal mucosa, periodontal ligament, bone-marrow, reticular cells of lymph nodes, capillary and venular pericytes.[2,9]

Criteria for identification of myofibroblasts

Histological criteria include spindle-cell or stellate-cell morphology, pale eosinophilic and prominent cytoplasm,

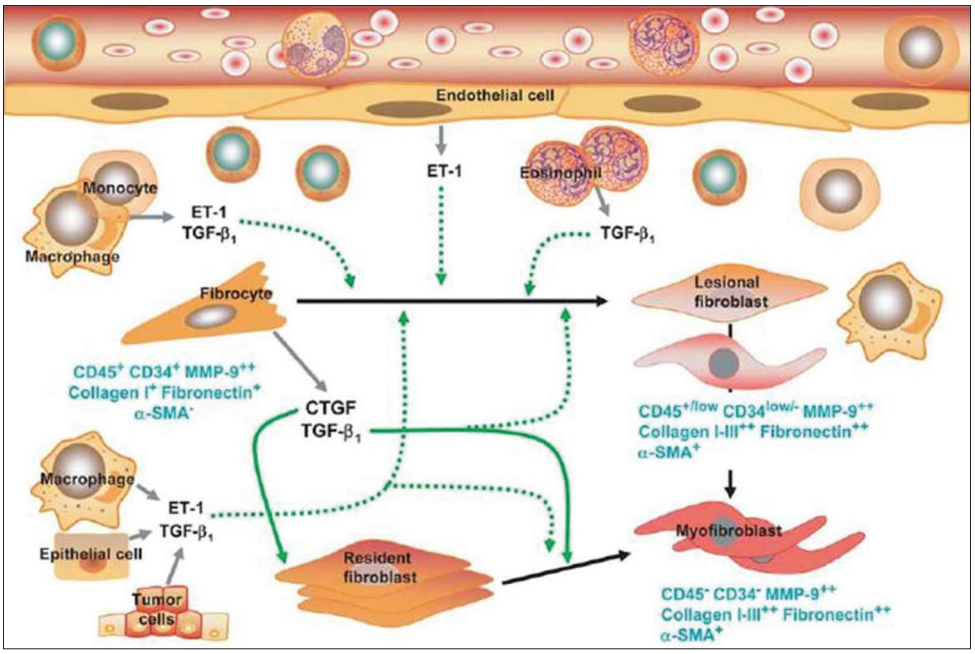

Figure 2: Formation of myofibroblasts from fibrocytes

pericellular matrix containing inter alia collagen and glycosaminoglycans.[1]

Ultrastructure criteria include prominent rough endoplasmic reticulum, Golgi apparatus producing collagen secretion granules, peripherally located myofilaments with focal densities, gap junctions, fibronexuses consisting of converging myofilament, external fibronectin fibril and absence of lamina.[1]

Immunophenotype criteria include Vimentin positive, α-SMA positive, Nonmuscle myosin positive, minimal levels of desmin and smooth-muscle myosin and extra domain A cellular fibronectin positive.[1]

Biochemical characteristics – Myofibroblasts possess synthetic property. They secrete collagens (Type I, III, IV and V), glycoproteins (e.g., fibronectins, laminins and tenascin), proteoglycans (e.g., aggrecan, synchrons, perlecan and decorin) and elastins, contributing to the majority of extracellular matrix.[3]

Classification

Based on immunohistochemical staining of the filaments, a classification system has been proposed

- V-type: Myofibroblasts that express only Vimentin
- VD-type: Myofibroblasts that express Vimentin and Desmin
- VAD-type: Myofibroblasts that express Vimentin, α-SMA, Desmin
- VA-type: Myofibroblasts that express Vimentin and α-SMA
- VM-type: Myofibroblasts that express Vimentin and Myosin.[9]

Myofibroblastic markers

α-SMA, Desmin, Vimentin, Paladin 41 g, Podoplanin, Stromelysin-3, Endosialin, Gamma-SMA, P4, Cadherin-11, GB-42, Tropomyosin-1, Thyl-1 and Cofilin[11,12]

Role of myofibroblasts in health and disease

Basically, the role of myofibroblasts can be broadly divided into physiological and pathological [Figure 3].

Role in growth and development

Myofibroblasts play an important role in organogenesis by the secretion of PDGF and SCF which promote the differentiation of embryonic stem cells.[9] After ligand binding, there are two separate intercellular signaling pathways for the PDGF receptor: a mitogen-activated protein kinase path and phosphatidylinositol 3-kinase path (PI3K). Depending on the cell types, one pathway may be required for cell activation and proliferation and the other for cell migration.[13]

Role in inflammation

Myofibroblasts play a major role in the inflammatory response. They do so by secreting mediators of inflammation, growth factors, by expression of their receptors and producing the interstitial matrix molecules, chemokines and cytokines and are also capable of augmenting or down-regulating the inflammatory response and synthesizing prostaglandins, expressing both the constitutive cyclooxygenase-1 gene product and inducible

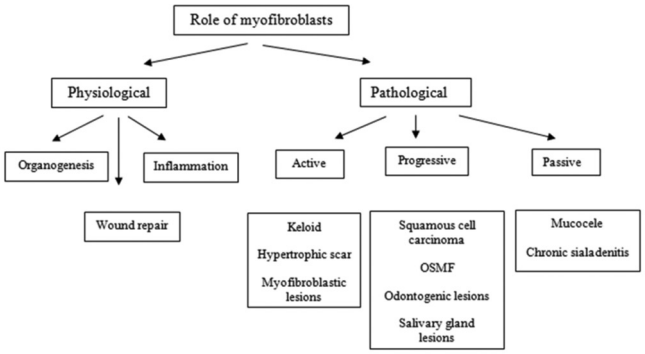

Figure 3: Role of myofibroblasts in health and disease

COX-2 protein. They even make both nitric oxide and carbon monoxide gases, important neurotransmitters and regulators of motility and inflammation.[2,8,9]

Role in wound repair

Myofibroblasts secrete collagen types I, III, IV and VIII, glycoproteins such as fibronectin and tenascin, laminin, chondroitin sulfate and matrix metalloproteinases-1, 2 and 3 (MMP-1, 2 and 3). Thereby myofibroblasts promote tissue remodeling following injury by involving in all three phases of wound healing.[14]

Role in epithelial dysplasia and oral squamous cell carcinoma

No myofibroblast differentiation has been found in histological investigations of potentially malignant disorders. This differentiation is seen only when the invasion occurs.[15] In the past, it was believed that the appearance of myofibroblasts was a host reaction meant to prevent invasion of malignant cells since myofibroblasts were abundant particularly at the invasive front. However, over the past 10 years, there is abundance of evidence suggesting that myofibroblasts essentially promote tumor invasion.[16] The appearance of myofibroblast depends on the development of oral squamous cell carcinoma (OSCC) and myofibroblast transdifferentiation depends on contact between OSCC cells and the stroma.[11]

Early and the key event in carcinogenesis is transdifferentiation of fibroblasts to myofibroblasts mediated by growth factors and cytokines expressed by tumor cells. In cancer, stromal deviations drive invasion and metastasis, the hallmarks of malignancy.[17]

The presence of stromal myofibroblasts is an effective predictor of OSCC mortality and is associated with aggressiveness regardless of tumor stage. The myofibroblasts presence varies among OSCC. This heterogeneity is due to disparity in TGF-β expression among OSCC. The presence of stromal myofibroblasts is significantly higher in high invasive OSSC than in low invasive OSCC. This suggests that myofibroblasts are associated with the creation of permissive environment for tumor invasion in OSCC and play an active role in metastasis.[18]

The myofibroblast differentiation in neoplasm is brought about by following:

- Changes in the composition and organization of the microenvironment associated with cytokines which are released by resident cells, inflammatory and tumor cells[17]
- Inactivation of JunD, a molecule protecting against oxidative stress, promotes myofibroblast differentiation[17]
- Reactive oxygen species (ROS) promotes conversion of fibroblasts into highly migrating myofibroblasts through accumulation of hypoxia-inducible factor-1α transcription factor and the CXCL12 chemokine[17]
- Tumor cells secrete PDGF-A, which acts as an fibroblast chemoattractants and thus contribute to the accumulation of activated fibroblasts in the tumor stroma[19]
- Epithelial-mesenchymal interactions, different growth factors released by malignant epithelial cells or numerous other processes may be responsible for the appearance of myofibroblasts.[15]

Following events helps in tumor invasion

- Myofibroblasts secrete numerous growth factors and inflammatory mediators that stimulate epithelial cell proliferation[9]
- Myofibroblasts suppress the cancer killing function of T cells[11]
- Malignant cells utilize the oxidative environment for their own advantage. Oxidative stress in tumors can be either intrinsic or extrinsic. TGF-β 1 increases the intracellular ROS level in stromal fibroblasts, which initiate changes in gene expression, leading to the secretion of hepatocyte growth factor, IL-6 and vascular endothelial growth factor (VEGF) that result in pro-invasive signals for migration of tumor cells[17]
- TGF-β converts α-SMA-negative fibroblasts that do not stimulate invasion into α-SMA-positive myofibroblasts that stimulate invasion.[11]

The cancer prompted formation of a myofibroblast network may serve as guidance structure which directs the migration of epithelial cancer cells. This is achieved by triggering the proteolysis and structural modification of the ECM, thereby creating channels that help the cancer cells in invasion.[11] As the stromal cells produce collagen

and ECM proteins, they also initiate the "desmoplastic reaction" to mediate the invasion.[20]

There are 2 mechanisms for stromal destruction: cancer-prompted destruction in low malignant SCC and cancer–stroma cooperative destruction in highly malignant SCC. The mesenchymal cells that mediate proteolytic activity in the stroma are myofibroblasts. Myofibroblast appearance in invasive cancer and tumor desmoplasia are important reflection of the tumor–host interaction, especially in aggressive cancers.[21] Myofibroblasts are present in the stroma of most human OSCC in two principal patterns, spindle and network.[15]

- In the network pattern, myofibroblasts are exceptionally abundant and occupy almost the entire tumor stroma
- The spindle pattern is characterized by stromal myofibroblasts that have spindle-shaped morphology and are located at the periphery of carcinomas as 1–3 concentric layers, a pattern that can also be found adjacent to a few or many tumor islands / nests.[15]

There is no significant difference in the presence of myofibroblast among different histological grades of SCC. This suggests that the transdifferentiation of myofibroblasts is induced during the invasive stage of SCC and further loss of tumor differentiation would not affect the number of these cells. The lack of myofibroblasts in normal and dysplastic oral epithelium and their characteristic appearance in SCC suggests that genetically altered epithelium may have an inductive effect on the adjacent stroma to produce myofibroblasts.[15]

Role in tumor angiogenesis and metastasis

Stromal myofibroblasts participate in the tumor angiogenesis Figure 4[21] by:

- Secreting proangiogenic growth factors (VEGF, bFGF, TGF-β, PDGFs, HGF, CTGF and IL-8)[20]
- Inducing MMPs in stromal myofibroblasts by the tumor derived factor, which further stimulates the angiogenesis[20]
- Recruiting endothelial cells and monocytes. The endothelial cells organize into new vessels and monocyes stimulate invasion[11]
- Regulating the inflammatory response within the tumor microenvironment, that will amplify its angiogenic program[11]
- Secreting chemokines which will stimulate carcinoma cell growth and promotes the recruitment of endothelial cells to the rim of the tumor. The organization of myofibroblasts at the borders of tumors with the neovasculature helps in the stabilization of tumor induced neovasculature.[21] Chemokines, growth factors and matrix-degrading enzymes act with immune cells resulting in breakdown of basement membrane barriers and attract tumor cells to distant sites. Chemokine CCL5 secreted by

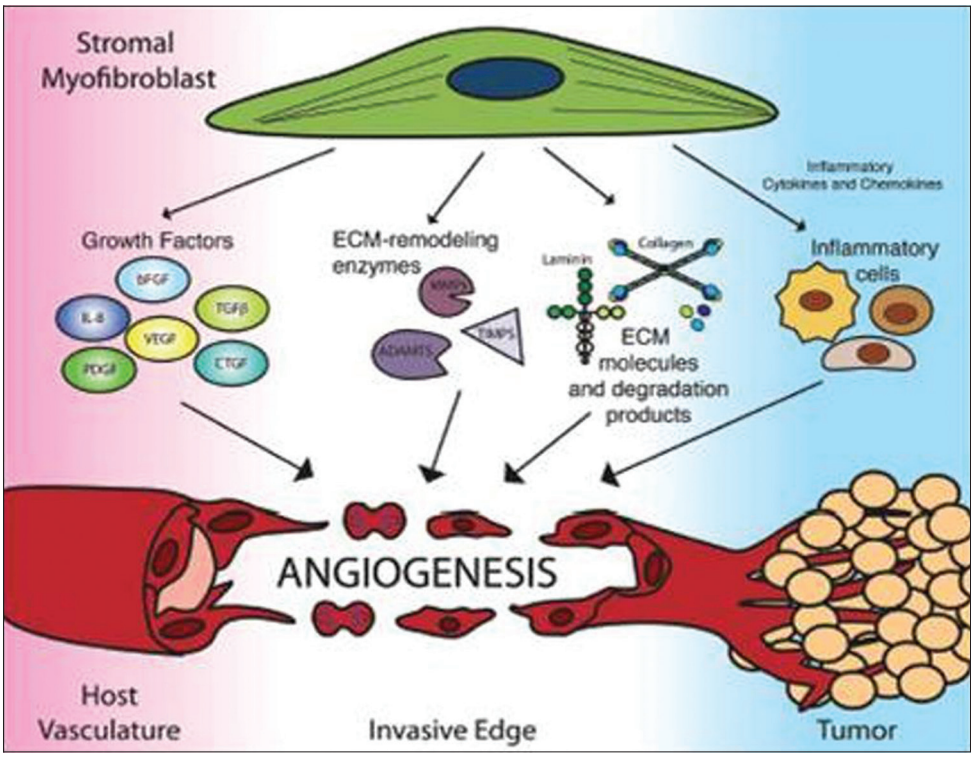

Figure 4: Stromal myofibroblasts modulate angiogenesis with a multiprong approach

myofibroblasts enhances their motility, invasion and metastasis.[19]

Reaction of myofibroblasts to cancer management

Myofibroblasts have been proposed as putative targets for therapy. There is a controversial issue whether or not, routine methods of cancer management may stimulate myofibroblasts and enhance invasion and metastasis.[11]

Surgical interventions cause wounds and stimulate myofibroblasts as part of the healing process. This makes a better niche for growth and invasion of cancer cells. To counteract this potential drawback, minimal surgical trauma and postoperative anti-inflammatory treatment should be considered.[11] Ionizing radiation (IR) stimulates the proinvasive activity of myofibroblasts. IR transforms fibroblasts into myofibroblasts at a dose of 1 Gy.[22] Chemotherapeutic agents such as cisplatinum or alkylating agents activate TGF-β thereby causing chronic inflammation and submucosal fibrosis in human.[11] Further researches are required to discover the therapeutic agents that can arrest the activity of tumor myofibroblasts.

Role in oral submucous fibrosis

Myofibroblasts are found to acquire an immune-privileged cell phenotype and are protected by apoptosis in chronic scarring processes due to killing of Fas + lymphocytes, permitting these cells to escape immune surveillance and thus continuous matrix synthesis.[23] The myofibroblast incidence increases progressively from normal, early oral submucous fibrosis (OSMF) to advanced OSMF with significant increase in advanced stages which is comparable to skin wounds, where only few myofibroblasts are present in early granulation tissue but numerous in later stages. Thereby, progression of OSMF from early to advanced stages can be considered to be kind of maturation mode of granulation tissue.[24]

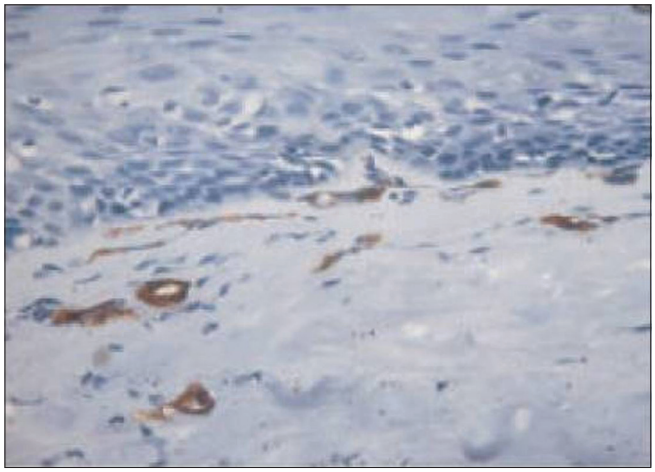

Figure 5: Few myofibroblasts are evident subepithelially in early OSMF.

OSMF actually represents failed wound healing process of the oral mucosa after chronic sustained injury resulting in scarring and fibrosis, which is in response to the hypersensitivity caused by arecoline and the resultant persistent juxta-epithelial inflammatory response, which acts as an initiating factor leading to a defective inflammatory response and activation of fibroblasts culminating in fibrosis.[24] TGF-β, a potent pro-inflammatory and pro-fibrotic cytokine, a main molecule related to imbalance between collagen deposition and degradation in OSMF is activated in response to arecoline challenge. Also there is increased expression of α5 β6 integrin in OSMF which promotes myofibroblast differentiation by activating TGF-β. The myofibroblast production and persistence could be one of the mechanisms by which TGF-β may contribute to fibrotic response in OSMF.[25] OSMF is also characterized by malignant transformation of about 7%–13% in the background of fibrosis. The cancer development and progression is facilitated by epithelial and stromal interactions. The stroma is characterized by marked alteration of fibroblast phenotype into myofibroblasts that express α-SMA [Figures 5 and 6],[24] which have been implicated in carcinogenesis, tumor progression and invasion.[24]

Role in odontogenic lesions

Earlier myofibroblasts were found in wall of odontogenic cysts and considered as the part of a homeostatic response to distension caused by cyst enlargement by Morgan PR *et al*.[25]

Later, staining of collagen fibers in the odontogenic keratocyst (OKC) and odontogenic neoplasms were found similar which suggests that the stroma in the OKC cannot be regarded just as structural support of the cyst wall, but its part in the neoplastic behavior can be considered. The stroma

Figure 6: Numerous myofibroblasts arranged parallel to the epithelium seen in advanced OSMF.

is essential for the maintenance of the epithelial tissues. Both make up an ecosystem in which continuous molecular cross talk between the participating cells is present.[16]

Appearance of myofibroblasts in stroma is a neoplastic phenomenon due to the TGF-β and PDGF secreted by neoplastic cells at a proinvasive state. TGF-β1 is strongly chemotactic for fibroblasts even at very low concentration. As fibroblasts migrate toward the cancer cells that secrete TGF-β1, fibroblasts will come across higher concentrations of TGF-β1 further leading to their transdifferentiation into myofibroblasts. Numerous growth factors, angiogenic factors, extracellular matrix components and proteinases are in turn produced, all together promote invasion and growth of neoplastic epithelial cells.[16]

Among the odontogenic cysts, odontogenic keratocyst [Figure 7] has highest number of myofibroblasts and dentigerous cyst has the lowest. Among the odontogenic tumors, ameloblastoma [Figure 7][16] has got significantly higher number of myofibroblasts than in unicystic ameloblastoma. Thereby myofibroblasts in the stroma of odontogenic cysts and tumors contribute to variations in the biological behavior of lesions. Thus, a positive association can be made between the presence of more number of myofibroblasts in the stroma and aggressive behavior of the odontogenic cyst/tumor. Thereby, myofibroblasts contribute to bone resorption, thereby favoring the progression and growth of these lesions.[16]

Role in Salivary gland lesions and tumors

Myofibroblasts were found in salivary gland neoplasms and their presence was co-related to the degree of invasion. Density of stromal myofibroblasts is attributed to the aggressiveness of the tumor.[26]

α-SMA positive stromal myofibroblasts were found in adenoid cystic carcinoma at the tumor invasion front and periphery of cribriform areas. In mucoepidermoid carcinoma and polymorphous low grade carcinoma, α-SMA was positive for stromal myofibroblasts in tumor invasion front but in pleomorphic adenoma occasional positivity was found. Epithelial-mesenchymal interaction found between malignant epithelial cells and stromal fibroblasts is the reason for presence of myofibroblasts, which contributes to aggressiveness of tumors. Hence, presence of numerous stromal myofibroblast in adenoid cystic carcinoma and mucoepidermoid carcinoma is the factor influencing the malignant potential of the tumor. In polymorphous low grade adenocarcinoma moderate numbers of stromal myofibroblast were seen, attributing to its low grade malignancy. In pleomorphic adenoma, absence of stromal myofibroblasts correlates with its slow growing and benign nature. The stromal myofibroblasts could be demonstrated only in the tumors with malignant potential. The density of these cells at the invasive front acts as a prognostic marker and predicts the aggressiveness of the lesion [Table 1].[26] Myofibroblasts are also seen in mucocele and chronic sialadenitis, the presence of myofibroblasts indicates a muscular supportive role around the cystic wall of mucous retention cysts and distended excretory ducts.[27]

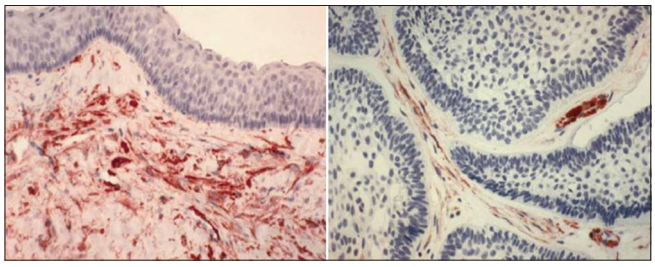

Figure 7: α- SMA expression by myofibroblasts in parakeratinized OKC and solid ameloblastoma

WORKING CLASSIFICATION OF MYOFIBROBLASTIC LESIONS OCCURRING IN HEAD AND NECK REGION

Reactive lesions

- Keloid
- Hypertrophic scar.

Neoplasms

Benign neoplasms

- Nodular fasciitis
- Proliferative fasciitis and proliferative myositis
- Myofibroma/myofibromatosis
- Inflammatory myofibroblastic tumor
- Cellular benign fibrous histiocytoma
- Nasopharyngeal angiofibroma.

Intermediate malignancy

- Desmoid type fibromatosis
- Plexiform fibrous histiocytoma.

Malignant lesions

- Infantile fibrosarcoma
- Adult fibrosarcoma
- Pleomorphic malignant fibrous histiocytoma
- Low grade myofibroblastic sarcoma [Table 2].

Table 1: Smooth muscle actin positivity and density of stromal myofibroblasts

Tumors	SMA positivity	Density
Pleomorphic adenoma	Occasional	Absence
Adenoid cystic carcinoma	Positive	High
Mucoepidermoid carcinoma	Positive	High
Polymorphous low grade adenocarcinoma	Positive	Moderate

SMA: Smooth muscle actin

Table 2: Myofibroblastic lesions with brief clinical, histopathological and immunohistochemical characteristics

Condition	Age	Sex	Site	Histopathology	IHC
Nodular fasciitis[28,29]	New born to 80 years	No sex predilection	Face and forehead	Feathery appearance Stroma is hypercellular with spindle shaped fibroblasts/myofibroblasts, lack nuclear hyperchromasia and pleomorphism, mitotic figures are plentiful	SMA positive Desmin positive/ negative
PF and PM[28,30]	40-60 years	No sex predilection	Head and neck region - rarely involved	PF - presence of large cells with abundant basophilic cytoplasm and nucleus with one to two prominent nucleoli giving ganglion cell appearance in the background of myxoid stoma PM - spindle cell fibroblastic proliferation surrounds and separates large group of muscle fibers creating a checkerboard like pattern	SMA positive MSA positive Desmin negative
Myofibroma/ myofibromatosis[28,30,31]	First 2 years of life	Male predilection	Scalp, orbit, parotid region, tongue, eyelid, retromolar region, buccal mucosa, nasal ala, face, gingiva, anterior floor of mouth and mandible	Peripheral zone is fascicular, myxoid to hyalinized or chondroid-appearing Central zone is cellular organized like hemangiopericytoma like vasculature Necrosis, vascular invasion and mitotic activity may be present Tumors in children consist entirely of the cellular component. In adults, the pattern of zones may be reversed with myxoid zone in the center of the lesion and cellular zone at the periphery	SMA positive Desmin negative The more primitive appearing central zone-actin is negative
Inflammatory myofibroblastic tumor[28,32]	Children and young adults	Female predilection	Epiglottis, maxillary sinus, major salivary glands and oral cavity (buccal mucosa)	Three basic patterns 1. Resembling granulation tissue, nodular fasciitis, or other reactive processes 2. Resembling a fibromatosis, fibrous histiocytoma, or a smooth muscle neoplasm 3. Resembling a scar or desmoid-type fibromatosis	Vimentin positive SMA and MSA vary from focal to diffuse pattern Cytokeratin positive (1/3rd of cases)
Cellular benign fibrous histiocytoma[28,31]	Young and middle aged adults	Male predilection	Head and neck region - rare <1%	Well circumscribed with epidermal hyperplasia and peripheral collagen trapping. More cellular, exhibiting predominantly fascicular or storiform pattern with multinucleated giant cells. Mitotic figures are common (10/10 HPF). Central necrosis is noted	SMA positive Tram track appearance
Nasopharyngeal angiofibroma[33-35]	Adolescent boys and young men 10-20 years	Male predilection	Superolateral nasopharyngeal area	The fibrous stroma is dense, parallelly arranged collagen fibers show hyalinization and focal area of myxoid change. Vascular channels seen are slit-like or dilated with variable thickness. Peripheral vessels are larger and arterial type with visible elastic lamina and central smaller vessels with thin elastic lamina	Endothelial cells (factor VIII related antigen positive, CD31 negative, CD34 negative) Perivascular cells (SMA positive) spindle/stellate cells (vimentin positive SMA positive/negative)
Desmoid type fibromatosis[30,31]	Middle aged females even during pregnancy	Female predilection	Head and neck region <10%	Infiltrative and proliferative cytologically bland fibroblast to myofibroblast appearing spindled cells arranged in long sweeping fascicles. Periphery of the lesion shows patchy chronic inflammatory cell infiltrate. Myxoid change or keloid collagen can be seen in some cases. Necrosis is absent	SMA positive Tram track appearance Desmin negative
Plexiform fibrous histiocytoma[36,37]	2-70 years	Female predilection	Head and neck region - rarely involved worms in sack presentation on palpation	Three patterns Fibrohistiocytic subtype Fibroblastic subtype Mixed subtype	Spindle cell SMA positive Round cells and osteoclasts CD68 positive

Contd...

Table 2: Contd...

Condition	Age	Sex	Site	Histopathology	IHC
Low grade myofibroblastic sarcoma[38,39]	Average age is 40 years	Male predilection	Head and neck region (tongue)	Spindle cells are arranged in interlacing fascicles. Central part of the tumor have edema with pseudomyxoid and microcystic areas and the inner and peripheral parts with thick bundles of collagen fibers and local hyalinization	Actin positive/negative desmin positive/negative Fibronectin positive calponin positive CD34, CD99 and CD117 positive
Infantile fibrosarcoma[40]	Infants and very young children	Male predilection	Head and neck region (16%)	Cellular neoplasm composed of intersecting fascicles of primitive ovoid and spindle cells arranged in a herringbone pattern or forming interlacing cords, bands or sheets of cells. Zonal necrosis or hemorrhage are present. Mitotically active and exhibit mild pleomorphism. Dystrophic calcifications present	Vimentin positive SMA positive/negative MSA positive/negative
Adult fibrosarcoma[41]	Middle aged adults	No sex predilection	Soft tissues of neck and paranasal air sinuses	Diffusely infiltrative, highly cellular arranged in sweeping fascicles that area angled in a chevron-like or herringbone pattern. Mitotic activity present. Multinucleated giant cells seen. Stroma varies from delicate to keloid like	Vimentin positive SMA positive/negative focally
Pleomorphic malignant fibrous histocytoma[42]	Late adulthood	Male predilection	Head and neck 5%-6% maxilla, mandible and maxillary sinus	Fascicular or storiform appearance Characteristic curvilinear, thick walled vessels are seen with the neoplastic cells usually in myxoid areas often appearing to radiate from these blood vessels giving a Christmas tree pattern	Actin positive Desmin positive Vimentin positive

SMA: Smooth muscle actin, IHC: Immunohistochemistry, MSA: Muscle-specific actin, PF: Proliferative fasciitis, PM: Proliferative myositis, HPF: High power field

CONCLUSION

Myofibroblast can be placed between a fibroblast and a smooth muscle cell in differentiation. It has constructive role in growth, development, inflammation and tissue repair. However myofibroblast also have a destructive role by helping in progression of disease in squamous cell carcinoma, OSMF, salivary gland lesions and odontogenic lesions. Myofibroblasts have passive role in mucocele and chronic sialedenitis.

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Conflicts of interest
There are no conflicts of interest.

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