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Myofibroblast - The Master Regulator – A Review Article

[1] Prasanna Nichat
[2] Himanshu Aeran
[3] Poonam Goel
[4] Gaurav Vidhale
[1] Reader, Dept. Of Oral Pathology
[2] Prof &Head, Dept. Of Prosthodontics
[3] Senior Lecturer , Dept. Of Oral Pathology
Seema Dental College & Hospital, Rishikesh
[4] Senior Lecturer, Dept. Of Oral Pathology
V.Y.W.S, Amrawati, Maharashtra
Address For Correspondence:
Dr. Himanshu Aeran, Director Principal
Seema Dental College & Hospital,
Virbhadra Road, Rishikesh
Phone number: +91- 9837063005
Email ID : drhimanu@yahoo.com
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Abstract
The myofibroblast is a distinctive cell for a number of reasons. During wound-healing, it can promote health, but it also has role in tumerogenesis n its progression. Its biological complexity makes it difficult to define. First, it is it is not found in normal untraumatised tissues,it doesn't constitute the normal essential cells of body. Second,it exhibits two phenotypes – the fibroblastic and smooth-muscle cell.

Key Words
myofibroblast, wound healing, tumor stroma

Introduction

Gabbani, who is an pioneer in this field, discovered these cell.[1] The myofibroblast contributes to mentain the integrity of mammalian tissue. It can also threaten health by promoting tumour development. It is also noted in most of the mammalian lesions, but typically not seen in normal untraumatised tissues. [2] This has contributed to difficulties in appreciating the nature of the myofibroblast and defining it.

Discovery of Myofibroblast

In year 1971, Myofibroblasts were, discovered in electron micrographs from experimental granulation tissue. The cell exhibited the characteristic of both fibroblast and the smooth muscle cell. Subsequently it was found to be essential for wound contraction. In subsequent studies it was termed as myofibroblast and the positivity for human smooth muscle actin antibody was reported. [3]

Structure of myofibroblast

Grinell in 1994 Gabbiani 1998 and many others have described the myofibroblast in simplest term as a differentiated fibroblast that exhibit charecteristics of smooth muscle. [4]

Histological Appearance:

Although myofibroblasts are morphologically best defined with the electron microscope, in routine paraffin sections,they are usually large, spindle shaped, often stellate (spiderlike) and reveal long cytoplasmic extensions with distinct acidophilic and fibrillar cytoplasm. Their nuclei are indented or show strangulations of nuclear segments. In poorly collagenized areas well developed myofibrolasts are seen. In heavy collagenized zones, these cess are less in number and correspond ultrastructurally, to poorly developed myofibroblasts or to fibroblasts.[3]
Ultrastructurally it shows features that includes well developed rough endoplasmic reticulum and golgi apparatus, peripheral myofilaments and cell to matrix junction known as Fibronexus. [5]
The cytoskeleton shows numerous bundles of microfilaments (stress fibers)[1] arranged parallel to the long axis of the cell and sometimes, in continuity with dense bands or plasmalemmal attachment plaques.
Deep nuclear indentations are seen ultra structurally that has been correlated with cellular contraction in several systems. Nuclear bodies are often present and nucleoli are conspicuous. [1]

The immunophenotypical characters

The myofibroblast is characterized by simultaneous expression of vimentin, smooth muscle actin, desmin and myosin heavy chain. [6]
Depending upon the expression patterns of the intermediate filaments and myosin myofibroblast can be of following types
VA (express actin and vimentin),
VAD (vimentin, actin, and desmin),
VADM (vimentin, actin, desmin, myosin)

Origin of myofibroblast

Myofibroblast is said to have multiple origin. To explain it three types of cells have suggested:
The fibroblast, the smooth muscle cell and the pericyte.
In granulation tissue, the myofibroblast have been shown to have originated from resident fibroblast in connective tissue. These are recruited at the site of injury by the process of chemotaxis and migration. pericytes or vascular SM cells around vessels are also considered as one more source for myofibroblast. [7]
The endothelial cells are also said be a source of myofibrobast via endothelial to mesenchymal it was seen in cardiac fibrosis cases, this transition gives rise to myofibroblast.[8]
However, the other mechanisms includes the recruitment from bone-marrow-derived circulating fibrocytes (BMDCF) and epithelial-to-mesenchymal transformation (EMT).[9] Bone-marrow-derived circulating fibrocytes under the influence of the local micro-environment, appear to become myofibroblasts.[10] The circulating fibrocyte represents the novel leucocyte subpopulation. These cells also form an important source of fibroblast during the healing of extensive burns wound where it may be difficult for a local fibroblast to

migrate from the edges of injury. Also recently it has been shown that bone marrow derived myofibroblast forms a major cellular component in tumor microenvironment. [11]

In other pathological conditions, epithelial mesenchymal transition is another possible source. For example, fibrosing conditions like renal fibrosis, idiopathic pulmonary fibrosis and liver fibrosis. [12]

Biologic role of Myofibroblast

In general, during organogenesis or morphogenesis , through mesenchymal-epithelial interactions, myo?broblasts are key player. Imflammatory mediators, growth factors and expression of their receptors along with secretion and formation of interstitial matrix and/or basement membrane proteins, all these factors which are required during organogenesis are are secreted by myofibroblast.[13] With formation of formation of the extracellular matrix (ECM), by proliferation and differentiation of epithelial, vascular and neurogenic elements they play a central role in wound healing. [14]

In the in?ammatory response they perform a major role by secreting both chemokines and cytokines. Thus they can augment or downregulate the in?ammatory reaction.[14] Myofibroblasts also synthesize prostaglandins, expressing both the constitutive cyclooxygenase-1 (COX-1) gene product and the inducible COX-2 protein. The formation nitric oxide and carbon monoxide which are the important neurotransmitters these cell regulates the motility and in?ammation.[15] Phenotypically activated myofibroblastalso express adhesion molecules such as intracellular adhesion molecule-1, vascular cell adhesion molecule, and neural cell adhesion molecule. Thus these cells may also orchestrate many immunologically mediated processes and inflammatory reaction by fostering the accumulation of lymphocytes, mast cells, and neutrophils. [15] The production of extra cellular matrix molecules such as collagen, glycosaminoglycans, tenascin, and ?bronectin in the interstitial space or basement membrane is part of the structure, growth, differentiation, and wound healing function of myo?broblasts. Tissue fibrosis occur if there any disturbance in above process. Therefore, ?brotic disease is a major pathological end point of activated and proliferating myo?broblasts in most of the tissues. [15]

Myofibroblast during Tissue Repair

It is generally accepted during wound healing and tissue repair that the key event is fibroblast-to-myofibroblast differentiation. [16]

Fibroblasts into myofibroblasts transition, during wound healing, is a two-step process:

1. The resident fibroblasts acquire a migratory phenotype by de novo developing contractile bundles composed of cytoplasmic actins. This cytoskeletal machinery generate comparably small traction forces.[17]
2. The remolding activity in the damaged tissue, increases stress in the extra cellular matrix. This further leads to development into ''differentiated myofibroblasts'' by expressing a smooth muscle actin (α-SMA). Alpha SMA is the most widely used myofibroblast marker. By the joint action of growth factors like transforming growth factor (TGFβ1),ECM proteins like the fibronectin (FN) splice variant that is (extra domain)ED-A Fibrinectin. The expression of α SMA is regulated.[18],[19]

Among the various chemical mediators TGFβ1 is considered to be major growth factor for myofibroblastic differentiation. TGF β1 has direct effect and induces α smooth muscle actin expression, formation of extracellular matrix protein and number of cytoskeletal protein that construct the myofibroblast contractile apparatus. [20]

Myofibroblast in the tumors stroma

Epithelial mesenchymal interaction involved right from embryogenesis to the mentainance of the healthy tissue structure. These coordinated epithelial – mesenchymal interactions are fundamentally controlling the growth and differentiation in normal and pathological situations including the tumor stroma. [21]

Tumor microenvironment constitutes of non-transformed cells and a specialised Extracellular matrix. The cells found within the stroma include fibroblasts, myofibroblasts, leukocytes, endothelial cells and bone marrow-derived cells, all of which collaborate to create the complexity of the tumour microenvironment.[21]

The fibroblast contributing to the tumor stroma is a predominant cell type. It has been termed as peritumoral fibroblast, carcinoma associated or tumor associated fibroblast or myofibroblast. In general this fibroblastic population in the stroma express good amount of α-smooth muscle actin marking the full differentiation of myofibroblast.[21]

Myofibroblasts are not observed in in situ carcinomas, suggesting that invasion beyond the basal lamina is required to evoke a myofibroblastic stromal reaction.[22] These cells are notably absent within the carcinomas lacking significant stromal desmoplasia. Desmplastic phenotype of a tumor stroma is associated with excessive formation of extracellular matrix. Although desmoplasia is generally considered as a response of host cells to inductive stimuli exerted by tumor cells, recent findings argue that stroma cells have the ability to participate actively in tumor progression by secretion of proteolytic enzymes, thus allowing invasion and metastasis. it is now well admitted that an important proportion of such enzymes is produced by stroma myofibroblasts as a host response to tumor.[22]

Different myofibroblast subpopulations can secrete growth factors, including transforming growth factor (TGF)-β, platelet-derived growth factors (PDGF), basic fibroblast growth factor, hepatocyte growth factor (HGF), keratinocyte growth factor, stem cell factor, epithelial growth factor, granulocyte/macrophage colony stimulating factor, and other cytokines. Myofibroblasts in tumors also express tissue factor, the cellular initiator of the protease blood coagulation cascade leading to the formation of thrombin.[21]

Stromal myofibroblast in tumors secrete elevated levels of the cytokine SDF-1 that stimulates carcinoma cell proliferation in vivo, acting through the CXCR4 receptor expressed on the surface of carcinoma cells. These studies highlight the importance of stroma-derived SDF-1/CXCR4 and TGF-β paracrine signalling in promoting tumourigenesis. Such specific communication across the tumor cell and the stromal cell are important and its understanding is essential.[22]

In addition, these stromal myofibroblast also secrete increased levels of ECM-degrading proteases such as matrix metalloproteinase 2 (MMP2), MMP3 and MMP9, facilitating increased ECM

turnover and altered ECM composition.[21] These Activated fibroblasts often secrete increased amounts of growth factors such as hepatocyte growth factor (HGF), insulin-like growth factor (IGF), nerve growth factor (NGF), WNT1, EGF and FGF2, which can induce proliferative signals within adjacent epithelial cells.[24] Activated fibroblasts also have an important role as modulators of the immune response following tissue injury, through the secretion of cytokines such as interleukin-1 and chemokines such as monocyte chemotactic protein. [24]

This cross talk between the tumor cells and myofibroblast and between myofibroblast and other stromal cell oraganises the series of events leading to successful malignancy and its progression. The cross talk in the form of soluble factors is a key for further research. Identification of these soluble factors should lead to the elucidation of this complex process. Such understanding not only will increase the understanding of tumor biology but also it will give us the new dimension of therapeutic approach targeting the stromal component of tumor

Conclusion

The myofibroblast is essential for integrity of mammalian body by virtue of its role of healing.

Its capacity to aggrendize the tumor development is extensively studied but exact role is yet to be elucidated. The detailed understanding of its role is necessary for exploring its therapeutic measures in cancers.

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