Myofibroblast- The Unique Cell- A Review Article

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ABSTRACT

Wound healing and fibrocontractive diseases are characterized by the presence of a cell called myofibroblast that is responsible for pathological tissue remodeling. Carcinogenesis is accompanied by a number of changes in the adjacent stroma including the appearance of myofibroblasts. The high contractile force generated by myofibroblasts is beneficial for physiological tissue remodeling but detrimental for tissue function when it becomes excessive such as in hypertrophic scars, in virtually all fibrotic diseases and during stroma reaction to tumors. The present review focuses on introduction, functions and origin of myofibroblasts and their role in various oral diseases.

Key words: Myofibroblast, wound healing, carcinogenesis, OSCC, odontogenic tumors

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INTRODUCTION

Myofibroblasts (MF) are fibroblasts with smooth muscle-like features characterized by the presence of a contractile apparatus.[1,2] 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[3]. Ultra-structurally, it has bundles of cytoplasmic microfilaments with dense bodies running parallel to the long axis, a well developed rough endoplasmic reticulum and Golgi apparatus, a notched nucleus, pinocytic vesicles, partial investment by basal lamina with points of plasmalemmal attachment, well developed microtendons and intercellular intermediate and gap junction.[4] α Smooth muscle actin (αSMA) is commonly regarded as the most important marker for the myofibroblast[5]. 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.[6] Myofibroblasts are classically involved in wound healing, but they are also found in the reactive tumor stroma.[7,8]

Origin of the Myofibroblast:

Myofibroblasts of wound tissue have been assumed to originate from local recruitment of fibroblasts in the surrounding dermis and subcutaneous tissue [9]. This is supported by the presence of many fibroblasts showing proliferation

marker-positive nuclei at the periphery of the wound. Another possible source of myofibroblasts is represented by pericytes or vascular SM cells around vessels. In the last years, evidence has been provided suggesting the existence of circulating precursor cells, called fibrocytes, that migrate into the wound and contribute to the formation of the myofibroblastic population of granulation tissue [10].

Role of myofibroblasts in wound healing:

During proliferative phase of wound healing few fibroblasts differentiate into myofibroblasts,

that are mainly responsible for tissue contraction and production of extracellular matrix components. Fibroblasts under tension via the extracellular matrix also express TGFβ1. This mechanical tension stimulates fibroblasts to differentiate into proto-myofibroblasts by the development of stress fibres. Proto-myofibroblasts can differentiate into mature myofibroblasts in response to specific factors like TGβ1, ED-A fibronectin (ED-A FN) and mechanical tension. Myofibroblasts play significant roles in promoting extracellular matrix deposition (ECM) deposition, release of inflammatory mediators and epithelial injury, which are believed to be important factors in perpetuating the cycle of injury of fibrosis.[9] Once the wound is repaired, mature myofibroblasts disappear through apoptosis or by dedifferentiation. Myofibroblasts may exist in pathological conditions, such as hypertrophic scars.

Myofibroblasts in different diseases:

Role of myofibroblast in head and neck squamous cell carcinoma (H & N SCC)

Myofibroblasts secrete extracellular matrix molecules and degrading enzymes, angiogenic and pro- and anti-inflammatory factors, and stimulate epithelial cell proliferation and invasion, migration and neovascularization.[10] Myofibroblasts in oral squamous cell carcinoma (OSCC) induce proliferation via secretion of activin A, and promote invasion throughout secretion of matrix metalloproteinase (MMPs).[10] Members of the transforming growth factor β (TGF-β) family - PDGF, insulin-like growth factor II (IGF-II), and interleukin-4 (IL-4) - seem to be the main factor involved in the differentiation process of fibroblasts into myofibroblasts[11]. Vered et al.[12] carried out an experimental study on carcinogenesis with 4-Nitroquinoline 1-oxide (4NQO) in the tongue mucosa of Wistar rats and observed that in areas of normal, hyperkeratotic/ hyperplastic, and dysplastic epithelium, myofibroblasts were scarce or completely absent in the underlying connective tissue.

However, in areas of superficial basal cell or invasive carcinoma, a significant increase on the number of myofibroblasts was seen, with close

proximity between these cell types and malignant neoplastic cells. Marilena Vered[13] examined the pattern of distribution of the smooth muscle fibroblasts(SMF) in squamous cell carcinoma by immunohistochemically stained slides. The cases were classified according to two dominant patterns: "spindle" and "network". In the "spindle"pattern, visualization at low and medium power revealed stromal α-smooth muscle actin-stained myofibroblasts with a spindle-shape morphology tightly adhering to the periphery of the carcinoma islands/nests in one-to-three concentric layers.

In the "network" pattern, SMF were exceptionally abundant and had a plump appearance, and their proportion occasionally exceeded that of the carcinomatous component. They were organized in short-to medium-length intersecting bundles and, at a higher magnification, their high density gave the impression of multilayering, thus the term "network". He observed that malignant cells were more commonly found in tumors that displayed high numbers of SMF with a "network" pattern of distribution. Lewis et al.[14] demonstrated the presence of myofibroblasts in the vicinity of invasive SCC but not in benign mucosal polyps. These cells were also absent in the stroma distant from carcinomatous epithelial islands. Therapeutic targeting of myofibroblasts, their by products or factors responsible for their transdifferentiation from fibroblasts may be beneficial to OSCC patients.

Zidar *et al.*[20] describe that invasion beyond the basement membrane is necessary to evoke a myofibroblastic stromal reaction. Also, Kojc *et al.*[21] state that disappearance of CD34-positive stromal cells and appearance of SMA-positive stromal myofibroblast are associated with transformation of laryngeal squamous intraepithelial lesions to SCC.

Myofibroblasts in the Stroma of Odontogenic Cysts and Ameloblastoma:

F Mashhadiabbas[17] studied myofibroblasts immunohistochemically and ultrastructurally in the Stroma of Odontogenic Cysts and Ameloblastoma. The high frequency of stromal myofibroblast in the odontogenic keratocyst implies that myofibroblast can contribute to aggressive nature of this cyst, but between odontogenic cysts and ameloblastoma, the presence of stromal myofibroblast has no correlation with invasiveness. One study reported a recurrent infiltrative ameloblastoma whose stroma contained abundant myofibroblast and concluded that these cells accompany the invasive behavior of this tumor.[15]

Immunohistochemical markers for myofibroblast:

The most frequently employed myofibroblast marker is a-SMA, which evidently fails to distinguish between myofibroblasts and SMC in situations that exhibit mixed populations.[19] Smoothelin was suggested a late differentiation marker for SMC that is not expressed in myofibroblasts (van der Loop et al., 1996)[16]. Very recently, the 4Ig isoform of the stress fiber protein palladin has been proposed as novel marker for myofibroblast differentiation (Ro¨nty et al., 2006)[16]

Therapeutic use of myofibroblasts in future:

Blocking the latent TGF-β1-activating integrin αvβ5, inhibition of integrin α3, α11, αvβ3, and β1 were shown to block myofibroblast development and may be developed into future therapies.[22] Blocking specific integrins is a promising future strategy to control the development of myofibroblasts in fibrotic disorders.[22] Mechanical stress determines the stress fiber localization. Hence, releasing myofibroblasts from stress – for example, using the Ac-EEED peptide will have a profound and long term effect on myofibroblast persistence and may even induce myofibroblast apoptosis.[23]

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