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REVIEW ARTICLE

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Myofibroblasts and their relationship with oral squamous cell carcinoma

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Abstract

Myofibroblasts are hybrid-phenotype differentiated cells in between fibroblasts and smooth muscle cells. Due to their contractile features and ability to synthesize extracellular matrix components, cytokines, proteases, and proangiogenic factors, myofibroblasts have been implicated in the pathogenesis of fibrocontractive diseases and in the progression of many tumors, including oral squamous cell carcinoma (SCC).

Objective: To perform a literature review on the origin of myofibroblasts, their main morpho-physiological and immunohistochemical aspects, and to discuss the correlations with oral SCC.

Method: A search was made on the PUBMED database to select the main papers in the literature in English related to the subject, published between January 1991 and December 2011.

Conclusion: Myofibroblasts are an important component of the stroma of oral SCCs, although they are not present in all tumors. Abundant presence of myofibroblasts may be associated with local disease recurrence and decreased patient survival. However, given the relatively limited number of studies on the subject, further research is needed to clarify the molecular mechanisms by which myofibroblasts influence the biological behavior of oral SCC.

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INTRODUCTION

Neoplasms are made of tumor cells wrapped in a stroma constituted by blood vessels, fibroblasts, extracellular matrix (ECM), inflammatory cells and, occasionally, myofibroblasts[1-4]. Even though the stroma has been considered for a long time as a support tissue to neoplastic cells, recent evidence indicates that it has a role in promoting malignant phenotypes[2,4,5]. Stromal alterations are frequently seen in many types of neoplasms, including oral squamous cell carcinoma (SCC)[6].

Myofibroblasts were originally thought to be variants of fibroblasts present in the granulation response of the wound healing process, due to their contractile activity. Today, myofibroblasts are considered to be hybrid phenotype cells with fibroblast and smooth muscle tissue characteristics, capable of expressing α-smooth muscle actin (α-SMA), and characterized by intense synthesis of ECM proteins, growth factors - such as hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and keratinocyte growth factor (KGF) - and proteases[1,2,7,8].

Recent studies have shown that poorer prognosis in some tumor types is correlated with the presence of myofibroblasts in a neoplastic stroma[2,5,9]. An accepted explanation for such event is the ability of the products synthesized by these cells to modulate a number of biological events associated with malignancy, such as growth, differentiation, adhesion, migration, and tumor cell invasion[1,4,6,10,11].

Additionally, studies have indicated that myofibroblasts may be potential targets in the treatment of malignant disease[12-14]. Among the main advantages related to targeting myofibroblasts in cancer treatment is the increased genetic stability of these cells and their wide applicability in different tumor types[14]. Strategies suggested to prevent strong interaction between myofibroblasts and malignant neoplastic cells include the inhibition of the signaling pathways involved in myofibroblast recruitment and differentiation and direct eradication of this cell type[12,13].

Objective

This literature review aimed to look into the origin of myofibroblasts, their main morpho-physiological and immunohistochemical aspects, and to discuss the correlation between myofibroblasts and oral SCC.

METHOD

A search was made on database PUBMED using the following keywords based on the Medical Subject Headings (MeSH): *myofibroblasts, oral squamous cell carcinoma* and *immunohistochemistry*. Papers meeting the following criteria were included: a) data reported on myofibroblasts, their morpho-physiological and immunohistochemical aspects, and/or correlations between myofibroblasts and development/progression of oral SCC; b) study included *in vivo* or *in vitro* model; c) papers published between January 1991 and December 2011. Forty-three papers met the criteria and were selected for analysis.

LITERATURE REVIEW

Origin

The replacement or expansion of myofibroblasts, during homeostasis or disease, was originally believed to occur solely at the cost of the cell populations residing in the tissues, fibroblasts more particularly[15-17]. However, depending on the nature of the tissue and other characteristics of the microenvironment, several cell types may act as myofibroblast precursors, such as smooth muscle cells, pericytes[18,19], endothelial cells[15], pancreatic and hepatic stellate cells[4,15], adipocytes, and myoepithelial cells[4]. Studies have also shown other potential sources of myofibroblasts, including mesenchymal stem cells residing in the tissues, bone marrow-derived fibrocytes, and epithelial-mesenchymal transition[15-17,19,20].

The differentiation of fibroblasts residing in myofibroblasts is induced by paracrine signaling triggered by tissue repair or inflammation. 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[1,2,12]. Special attention is given to TGF-β1, a multifunctional peptide which regulates various cell activities, including growth and differentiation, and ECM macromolecule expression and metabolization[21,22]. TGF-β1 triggers the production of fibronectin by fibroblasts, which by its turn triggers the synthesis of α-SMA that is incorporated to stress fibers. Then new proteins are synthesized to allow molecular adhesion between α-SMA myofilaments, cytoplasmic membrane,