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The upregulation of insulin-like growth factor-1 in oral submucous fibrosis

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Summary Insulin-like growth factor-1 (IGF-1) is a member of a family of two interacting polypeptide hormone ligands with close homology to proinsulin. IGF-1 can influence mesenchymal cell migration, proliferation, and extracellular matrix deposition, thus implicating it in the progression of fibrotic disorders. Currently, there is limited information about the regulation of IGF-1 expression in areca quid-associated oral submucous fibrosis (OSF). The aim of this study was to compare IGF-1 expression in normal human buccal mucosa and OSF specimens and further explore the potential mechanism that may lead to induce IGF-1 expression. Twenty OSF specimens and 10 normal buccal mucosa were examined by immunohistochemistry. The activity of IGF-1 from cells cultured from OSF and normal buccal mucosa were by using reverse-transcriptase polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). Furthermore, the effect of arecoline, the major areca nut alkaloid, was added to explore the potential mechanism that may lead to induce IGF-1 expression. IGF-1 expression was significantly higher in OSF specimens ($p < 0.05$) and expressed mainly by fibroblasts, endothelial cells, and inflammatory cells. OSF demonstrated significantly higher IGF-1 protein expression than normal buccal mucosa fibroblast (BMF) both in mRNA and protein levels ($p < 0.05$). In addition, arecoline was also found to elevate IGF-1 mRNA and protein expression in a dose-dependent manner ($p < 0.05$). Taken together, the data presented here demonstrated that IGF-1 expression is significantly upregulated in

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OSF from areca quid chewers and arecoline may be responsible for the enhanced IGF-1 expression in vivo.
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Introduction

Oral submucous fibrosis (OSF) has been identified as a precancerous condition.[1] One of the clinical symptoms of OSF is trismus, a limitation of mouth opening. These may eventually impair the ability to eat and speak. Areca quid chewing has been recognized as one of the most important risk factors for OSF.[2,3]

The main histopathological characteristic of OSF is the deposition of collagen in the oral mucosa.[4,5] It has been found that arecoline, a major areca nut alkaloid, could stimulate human buccal mucosal fibroblasts (BMFs) proliferation[6,7] and collagen synthesis.[6] A reduced degradation of the α1(I) collagen trimer synthesized by OSF fibroblasts may induce the alteration of the ratio of α1(I):α2(I) chains.[8] The attendant increase of lysyl oxidase activity may also contribute to abnormal deposition of collagen in OSF.[9] Recently, our studies have shown that the upregulation of tissue inhibitor of metalloproteinase-1,[10] vimentin,[11] cyclooxygenase-2,[12] plasminogen activator inhibitor-1,[13] interleukin-6,[14] and keratinocyte growth factor-1[15] may contribute to the extracellular components accumulation in OSF. Despite above evidences, the pathogenesis of OSF related areca quid chewing still remains to be elucidated.

Insulin-like growth factor-1 (IGF-1) is a 70 amino acid, 7.6 kd, single-chain nonglycosylated polypeptide with structural similarity to insulin. It may act as an autocrine or paracrine growth hormone[16] and mediates most of the peripheral IGF-1 directly stimulates fibroblast proliferation and perhaps collagen synthesis.[17,18] IGF-1 is consistently and dramatically upregulated in a variety of fibrotic diseases, such as idiopathic pulmonary fibrosis,[19] systemic sclerosis [21] bleomycin-induced pulmonary fibrosis,[20] and carbon tetrachloride (CCl_4)-induced hepatic fibrosis.[22]

The biologic roles of IGF-1 induce cell proliferation and collagen synthesis, which may be important in fibroproliferative process in areca quid-associated OSF. The purpose of this study was to test whether IGF-1 expression regulated within OSF specimens and to further explore possible pathogenic mechanisms that might lead to enhanced expression of IGF-1 in vivo. More specifically, we also set out to explore where expression of IGF-1 can be triggered in human buccal mucosa fibroblasts (BMFs) stimulated by arecoline in vitro.

Materials and methods

Immunohistochemistry

Formalin-fixed, paraffin-embedded specimens of 10 normal buccal mucosa from non-areca quid chewers, and twenty OSF specimens from areca quid chewers, were drawn from the files of the Department of Pathology, Chung Shan Medical University Hospital. Diagnosis was based on histological examination of hematoxylin- and eosin-stained sections. Five micron sections were stained with the monoclonal anti-IGF-1 antibody (Santa Cruz Biotechnology, CA, USA) (1:100 dilution) using a standard avidin—biotin—peroxidase complex method.[23] AEC (DAKO, Carpinteria, USA) was then used as the substrate for localizing the antibody binding. Negative controls included serial sections from which either the primary or secondary antibodies were excluded. The preparations were counterstained with hematoxylin, mounted with Permount (Merck, Darmstadt, Germany) and examined by light microscopy.

Cell culture

Nine healthy individuals without areca quid chewing habits were selected from the Department of Oral Surgery (Chung Shan Medical University Hospital, Taichung, Taiwan) with the informed consent for this study. Biopsy specimens were derived from histologically normal areas of surgical third molar extraction from patients. The OSF specimens were obtained from 22 male patients with areca quid chewing habits during surgical biopsy. Clinical diagnosis was confirmed by histopathological

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