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Expression of estrogen receptors (ER) and human epidermal growth factor receptor 2 (HER2) in mucoepidermoid carcinoma: Relationship to its grading

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Abstract

Introduction: Mucoepidermoid carcinoma (MEC) is one of the most common malignant salivary gland neoplasms. It represents diverse biological aggressiveness and prognosis. Estrogen receptors (ER) are activated by sex hormone Estrogen. HER2 is a member of epidermal growth factor receptors. Both ER and HER2 have been implicated in the pathogenesis and prognosis of many neoplasms particularly breast. Little is known about their role in MEC.
Materials & methods: Normal salivary gland, low and high grade MEC tissue specimens were stained with anti-ER and anti-HER2 antibodies and the expression was quantified using ImagJ.
Results: Normal salivary gland tissues were negative for both ER and HER2 while MEC was positive for both of them. Interestingly, ER and HER2 expression was higher in high grade MEC than in low grade MEC.
Conclusion: ER and HER2 expression in MEC is correlated with its grade and may play a role in development and progression of MEC.

Keywords: ER; HER2; Mucoepidermoid carcinoma

1. Introduction

Benign and malignant salivary gland neoplasms constitute a significant part of oral tumors after squamous cell carcinoma [1]. Mucoepidermoid carcinoma (MEC) is considered one of the most common salivary gland malignancies and it is also the most common salivary gland malignancy in children [2].

MEC is believed to arise from the reserve cells of excretory ducts and the tumor consists of three cell types; mucous cells, epidermoid cells and intermediate cells [3]. As the results of considerable variations in type, distribution and growth pattern of MEC cells, several histological variants are seen; low, intermediate and high-grades [4].

MEC manifests diverse biological aggressiveness showing association with its histological grade and

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which has been demonstrated in many previous studies [1,5&,6].

Estrogen receptors (ER) are a group of proteins that are activated by the hormone estrogen and that have two different forms; alpha and beta [7]. Sun et al. demonstrated that ER might play different roles in the development of breast cancer [8].

Human epidermal growth factor receptor 2 (HER2) is a member of epidermal growth factor receptor family. It acts as oncogene, its overexpression has been shown to play an essential role in the development and progression of aggressive types of breast cancer [9]. Therefore, both ER and HER2 are the most frequently used molecular markers in breast cancer with different outcomes [10].

Mammary and salivary glands are tubuloacinar exocrine glands and share similar morphological characteristics. Comparing the tumors arising from these two different sites, similar histological features are observed. Although the cancers differ in incidence and clinical behavior, certain biological features identified in both entities have been described, and potential common therapeutic approaches have been considered [11].

In a previous study, expression of ER suggested that estrogen may have a biological role in oral mucosa and salivary glands [12]. The advent of sex hormone antagonists and their use in treatment of patients with ER positive breast carcinomas has prompted investigators to evaluate the expression of ER in a variety of tumors including those arising in salivary glands [13].

Moreover, HER2 expression was demonstrated in salivary gland carcinomas and that expression was dependent on type of carcinoma studied [14].

To the best of our knowledge, there are few reports regarding the expression of both ER and HER2 in MEC in particular. Therefore, the present study was undertaken to evaluate the expression of ER and HER2 in low and high-grade MEC in order to elucidate a possible role of either or both in development and progression of salivary MEC.

2. Materials and methods

2.1. Case selection

5 cases of normal salivary gland, 10 cases low and 10 cases high grade MECs were obtained from the archives of Oral Pathology Department, Faculty of Dentistry, Tanta University in the period from 2013 to 2014. H&E stained slides of low and high grade MEC were reviewed and confirmed for diagnosis. Normal salivary gland tissues were obtained from cases of mucocele.

2.2. Immunohistochemistry

Formalin fixed paraffin embedded (FFPE) blocks of normal salivary gland, low and high-grade MEC were cut into 4 um thick sections, de-paraffinized in xylene and rehydrated in descending grades of ethanol. Blocking of endogenous peroxidase activity was performed using methanol containing 0.3% of hydrogen peroxide for 30 min. Antigen retrieval was done using EDTA (PH8). Then, the sections were incubated with primary antibodies for one hour in a humid chamber (anti-ER antibody (cat# SP1 lab vision) at 1:100 concentrations and anti-HER2 antibody (cat# AB-17 lab vision) at 1:400 concentration). The slides were rinsed in phosphate buffered saline (PBS) and secondary antibody was applied at 1:1000 concentrations and incubated for 30 min. The sections were rinsed in PBS and covered by Diaminobenzidine (DAKO, Glostrup, Denmark) for detection of the reaction. The sections were then counterstained with Meyer's hematoxylin and dehydrated in ascending grades of ethanol. Finally, the slides were mounted and examined under light microscope. Taking in consideration the percentage of positive cells and the overall staining intensity, ER and HER2 were considered positive if over than 10% of cells showed strong or diffuse staining. ER and HER2 were considered negative if less than 10% of the cells showed weak or no staining [15].

2.3. Quantification of positive staining

Protein expression for both antigens was quantified in the study cases using ImageJ program. The quantification was performed in 3 different fields in each case and the average was calculated and used to represent level of expression. Expression level for both ER and HER2 in normal salivary gland, low and high grade MEC were blotted in graphs using Microsoft Excel 2010 program.

3. Results

3.1. ER expression

Estrogen antibody showed positive cytoplasmic expression in both low and high grade MEC. The expression intensity was higher in high grade than low grade. Normal salivary gland tissue was negative for estrogen except for positive staining at intercalated