Human Pathology (2015) **46**, 255–259

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Human PATHOLOGY

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Original contribution

A comparative analysis of LEF-1 in odontogenic and salivary tumors☆

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Received 30 July 2014; revised 28 October 2014; accepted 29 October 2014

Keywords:
LEF-1;
Lymphoid enhancer binding factor-1;
Salivary gland tumors;
Odontogenic tumors;
Basal cell adenocarcinoma;
Immunohistochemistry;
β-Catenin

Summary LEF-1 is a nuclear transcription factor of the Wnt pathway that regulates multipotent skin stem cell differentiation. β-Catenin is considered a transcriptional coactivator that interacts with LEF-1.This study evaluates LEF-1 in a variety of odontogenic and salivary tumors and determines the prevalence of β-catenin coexpression. Ninety-eight salivary gland tumors and 51 odontogenic tumors were evaluated for LEF-1 and β-catenin immunohistochemical staining. Positivity was defined as at least 2+ intensity in more than 50% of tumor cells, which required a composite score of 6 or more. LEF-1 was positive in 64% (7/11) of calcifying cystic odontogenic tumors (CCOT). Nuclear β-catenin was present in 82% (9/11) of CCOT. Coexpression of LEF-1 and nuclear β-catenin was noted in all LEF-1–positive CCOT. Strong and diffuse LEF-1 expression was seen in 69% (11/16) of basal cell adenocarcinomas (BCAC) and 63% (5/8) of basal cell adenomas (BA). Nuclear β-catenin was present in 50% (4/8) of BA and 43% (6/14) of BCAC. For BA, 4 of 5 LEF-1–positive tumors showed coexpression of β-catenin, and for BCAC, 5 of 9 LEF-1–positive tumors showed coexpression. In conclusion, this study documents for the first time the presence of LEF-1 expression and nuclear β-catenin coexpression in select basaloid salivary gland tumors and various odontogenic tumors. We demonstrate LEF-1 expression in both BA and BCAC preferentially over other salivary gland tumors suggesting some utility as a diagnostic marker.

1. Introduction

LEF-1 is a nuclear transcription factor of the Wnt pathway that regulates multipotent skin stem cell differentiation into epidermal keratinocytes, sebaceous glands, tooth development [1], hair follicles, and pre-B and T lymphocytes (but not in mature B-cells) [2]. LEF-1 expression is also required for odontogenesis and submucosal gland formation in the airway [3-5]. *CTNNB1* is a regulatory gene in this pathway that encodes β-catenin, a downstream transcriptional activator of Wnt. β-Catenin accumulates in the nucleus and forms complexes with DNA-binding proteins such as TCF and LEF-1 [6]. β-Catenin can thus be considered as a transcriptional coactivator that interacts with LEF-1 [7].

☆ Disclosures: The authors have no conflict of interest to report or funding sources to disclose.

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http://dx.doi.org/10.1016/j.humpath.2014.10.018
0046-8177/

Given the functional role in the aforementioned normal tissue types, β-catenin and LEF-1 make appealing markers to evaluate in skin adnexal, odontogenic, and salivary neoplasms. Some studies have demonstrated LEF-1 expression in basal cell carcinoma and pilomatrixomas [8,9]. However, LEF-1 expression has not been evaluated in odontogenic or salivary neoplasms, although interestingly, 70% of adamantinomatous craniopharyngiomas, often regarded as odontogenic tumor homologues, stained with LEF-1 [10]. On the other hand, β-catenin has been studied in greater detail, and nuclear expression has been documented in craniopharyngiomas, calcifying cystic odontogenic tumors (CCOT), and rare ameloblastomas. Interestingly, a study by Kawahara et al [11] has demonstrated some degree of nuclear expression of β-catenin in 95.4% (21 of 22) of salivary basal cell adenomas (BA) with localization in the basaloid myoepithelial cells and 33.3% (1/3) of basal cell adenocarcinomas (BCAC). All other 154 salivary gland tumors tested were negative for β-catenin, including pleomorphic adenomas, Warthin tumors, adenoid cystic carcinoma (ACC), epithelial myoepithelial carcinoma, polymorphous low-grade adenocarcinoma, salivary duct carcinoma, acinic cell carcinoma, and adenocarcinoma not otherwise specified. In addition to their tumorigenic implications, both markers may potentially help in improving diagnostic accuracy in classification of both salivary and odontogenic tumors, which may be challenging at times. We herein evaluate LEF-1 in a variety of odontogenic and salivary tumors and also determine the prevalence of β-catenin coexpression.

2. Material and methods

2.1. Case selection and immunohistochemical staining

After obtaining institutional review board approval (PRO08030186), 98 salivary gland tumors (8 BA, 12 pleomorphic adenomas, 2 carcinoma ex-pleomorphic adenomas, 16 BCAC, 22 ACC, 19 epithelial myoepithelial carcinomas, 8 mucoepidermoid carcinomas, 10 clear cell [hyalinizing] carcinomas, 1 intercalated duct hyperplasia evolving into BA) and 51 odontogenic tumors (13 ameloblastomas, 11 CCOT, 3 adenomatoid odontogenic tumors, 6 calcifying epithelial odontogenic tumors, 1 squamous odontogenic tumor, 3 ameloblastic carcinomas, 12 clear cell odontogenic carcinomas, 1 ameloblastic fibroma, 1 ameloblastic fibrosarcoma) were retrieved from the pathology archives. The histologic subtypes of the ameloblastomas included 7 plexiform and 6 follicular.

Immunohistochemical staining for LEF-1 (sc-8591, 1:200 dilution; Santa Cruz Biotechnology, Santa Cruz, CA) was performed on all cases. Immunohistochemical staining for β-catenin (M3539, 1:250 dilution; Dako, Carpinteria, CA) was performed to evaluate coexpression in tumor categories that had a high-frequency (>50%) LEF-1 positivity. Hair follicle bulb and lymph node were used as a positive control (Fig. 1A-C).

2.2. Scoring parameters

Nuclear staining intensity (grades 0-3) and percentage of positive cells were recorded. For LEF-1, a value between 1 and 4 was assigned for the percentage of positive cells (1 for 0%-25%, 2 for 26%-50%, 3 for 51%-75%, and 4 for 76%-100%). The product of intensity and positive cells was calculated for a composite score (range, 0-12). Positivity was defined as at least 2+ intensity in more than 50% of tumor cells, which required a composite score of 6 or more. For β-catenin, only nuclear expression was considered.

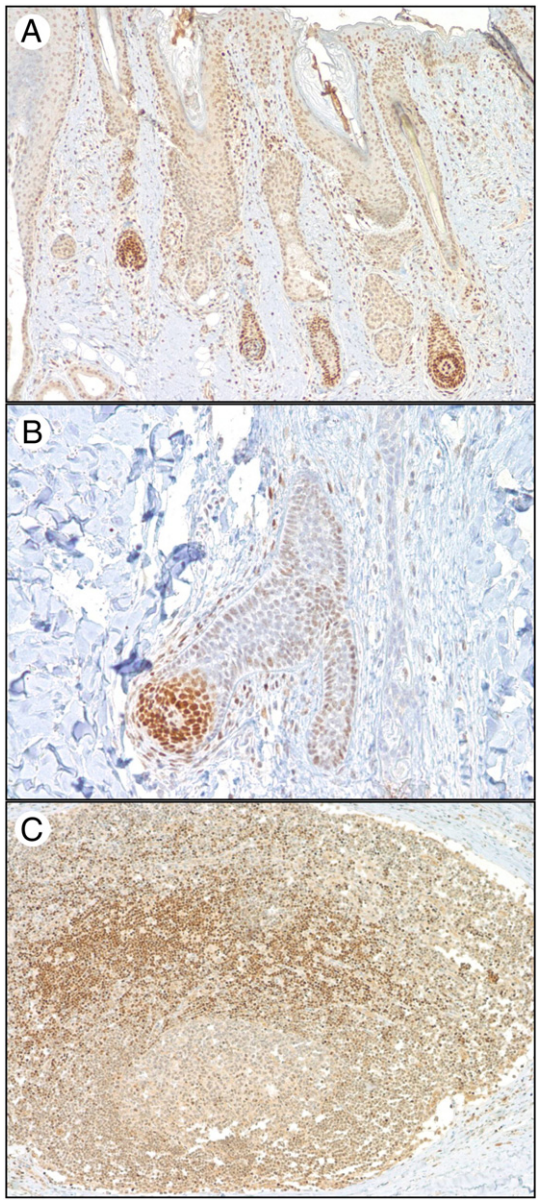

Fig. 1 Normal staining patterns of LEF-1: A, normal skin, original magnification ×40; B, hair bulb, ×200; C, germinal center, ×40.