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Clinical significance of TC21 overexpression in oral cancer

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BACKGROUND: In search of novel molecular markers for oral cancer, we reported increased levels of TC21/R-Ras2 transcripts in oral squamous cell carcinoma by differential display. The aim of this study was to determine the clinical significance of TC21 in oral cancer.

METHODS: Immunohistochemical analysis of TC21 protein expression was carried out in 120 leukoplakias, 83 OSCCs and 30 non-malignant tissues, confirmed by immunoblotting, and correlated with clinicopathological parameters as well as disease prognosis. Co-immunoprecipitation assays were carried out to identify the interaction partners of TC21 protein in oral cancer cells and tissues.

RESULTS: TC21 nuclear expression increased from normal oral tissues to leukoplakia and frank malignancy ($P < 0.001$). TC21 overexpression was observed in 74.2% leukoplakia with no dysplasia, 75.9% dysplasias and 79.5% OSCCs in comparison with normal oral tissues. Receiver operating characteristic analysis showed that the area-under-the curve values were 0.895, 0.885, and 0.919, while the positive predictive values were 95.8%, 95.6%, and 97.1%, for nuclear immunostaining for normal versus leukoplakia with no dysplasia, leukoplakic lesions with dysplasia, and OSCCs, respectively. Immunoblotting confirmed overexpression of TC21 in oral lesions. Using co-immunoprecipitation assays, we showed interactions of TC21 with Erk2, PI3-K, 14-3-3ζ and 14-3-3σ proteins in oral cancer cells.

CONCLUSION: Our findings suggested that alteration in TC21 expression is an early event in oral cancer and correlates with poor prognosis of OSCCs. TC21 interactions with Erk2, PI3-K, 14-3-3ζ and 14-3-3σ proteins in oral cancer cells and tissues suggests the involvement of TC21 in signaling pathways in oral cancer.

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Introduction

Head and neck squamous cell carcinoma (HNSCC), including the oral cavity and oropharynx, is the sixth most common cancer in the US and the fourth most prevalent cancer in men worldwide (1). Despite recent advances in surgery, radiation, and chemotherapy, the prognosis for head and neck cancer remains dismal, especially if malignant tumors are not diagnosed in early stages of the disease (2, 3). Currently, the most important conventional prognostic factors for survival of OSCC patients are histological tumor grade and tumor stage at the time of diagnosis, including depth of tumor invasion and involvement of regional lymph nodes. In addition to these clinicopathological parameters, biomarkers are being intensively sought and validated for oral cancer. Knowledge of molecular alterations in various stages of oral tumorigenesis will greatly help in identifying putative biomarkers for early diagnosis and as novel targets for therapeutic intervention. In search of such novel molecular markers, our laboratory reported increased levels of TC21 transcripts in OSCCs, using Differential Display reverse transcription-PCR (DD) in clinical specimens and cell lines (4).

TC21/R-Ras2 is a member of the Ras supergene family involved in diverse cellular functions including proliferation, differentiation, apoptosis, cytoskeletal