Göteborg, 2021

On factors associated with development of oral squamous cell carcinoma

Akademisk avhandling

Som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, fredagen den 10 december, klockan 13.00

av

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Avhandlingen baseras på följande delarbeten

I. Jäwert F, Nyman J, Olsson E, Adok C, Helmersson M, Öhman J. Regular clinical follow-up of oral potentially malignant disorders results in improved survival for patients who develop oral cancer. Oral Oncol. 2021;121:105469.

II. Jäwert F, Pettersson H, Jagefeldt E, Holmberg E, Kjeller G, Öhman J. Clinicopathologic factors associated with malignant transformation of oral leukoplakias: a retrospective cohort study. Int J Oral Maxillofac Surg. 2021;50(11):1422-1428.

III. Jäwert F, Fehr A, Öhman J, Stenman G, Kjeller G. Copy number profiling reveals recurrent oncogenic events in oral leukoplakias. *In manuscript* 2021.

IV. Jäwert F, Hasséus B, Kjeller G, Magnusson B, Sand L, Larsson L. Loss of 5-hydroxymethylcytosine and TET2 in oral squamous cell carcinoma. Anticancer Res. 2013;33(10):4325-8.

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On factors associated with development of oral squamous cell carcinoma

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Abstract

Oral squamous cell carcinoma (OSCC) has severe impacts on the affected patient's morbidity and mortality. Early detection of OSCC is of outmost importance to reduce morbidity and to improve patient survival. A significant fraction of all OSCCs is preceded by oral leukoplakia (OL). OL is clinically detectable as a more-or-less white patch in the oral mucosa. However, there is still limited knowledge regarding which patients with OL that will develop OSCC and how to best monitor and manage these patients. The overall aims of this thesis were to investigate clinical, histopathologic, genomic and epigenomic factors associated with OL progression to OSCC and to evaluate a follow-up program for these patients.

To assess if clinical follow-ups of OL patients result in early detection and high survival rate if cancer develops, a retrospective medical record and register-based study of 739 patients with OSCC was performed (**Paper I**). The results indicate that follow-ups of OL patients at an Oral and Maxillofacial Surgery - or Oral Medicine clinic results in early detection and improved survival, if the lesion transforms into cancer. Clinicopathologic features of OL that are associated with progression to OSCC were investigated in a retrospective medical record – and register-based study that included 234 patients (**Paper II**). The results showed that non-homogeneous OL progressed to OSCC to a significantly greater extent than homogeneous OLs. In addition, dysplastic OLs and OLs located at the tongue were associated with increased risk of progression to OSCC. Copy number alterations (CNAs) of known cancer driver genes were studied using fluorescence *in situ* hybridization (FISH) in OLs and OSCC (**Paper III**). CNAs in OLs that progressed to OSCC and the corresponding OSCC (N = 14) were analyzed. Comparisons were made with OLs that did not transform into OSCC (N = 14). The results showed that CNAs not only occur in OSCC but also in OLs. Some CNAs were detected somewhat more frequently in OLs that transformed into cancer. This indicates possible roles for CNAs of some genes in the development and progression of subsets of OLs. Epigenetic gene regulation mechanisms, such as DNA methylation, are involved in carcinogenesis. The epigenetic factors 5-methylcytosine (5mC), 5-hydroxymethylcytosine (5hmC) and ten-eleven-translocation-2 (TET2) were analyzed in OSCC (N = 15) and compared to healthy oral epithelium (N = 12) (**Paper IV**). Using immunohistochemistry, significantly lower levels of 5hmC and TET2 were detected in OSCCs compared to healthy oral epithelium.

In summary, this thesis highlights the importance of monitoring patients with OL, since it results in early detection and high survival rates, if cancer develops. In addition, we identify clinical, histopathologic, genomic and epigenomic factors that can, or have potential to, be used to identify patients with OL who are at high risk for cancer development. This knowledge may be used to identify patients who should be prioritized for regularly scheduled clinical examinations.

Keywords: oral leukoplakia, oral squamous cell carcinoma, malignant transformation, early diagnosis, genomic profiling, epigenomics

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