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The role of the tumour microenvironment in the biology of head and neck cancer: lessons from mobile tongue cancer

Marilena Vered, Dan Dayan and Tuula Salo

We read with great interest the Review by Leemans and colleagues (The molecular biology of head and neck cancer. *Nature Rev. Cancer* **11**, 9–22 (2011))[1] in which the authors extensively describe the genetic alterations that cause changes in signalling pathways in head and neck cancer, and in which they discuss the recent insights into the distinction between tumours of the head and neck that have a human papillomavirus (HPV)-associated aetiology and those that do not. It is our opinion that special attention should be given to the tongue, because it is the most common site for oral cancer in terms of epidemiology[2], and because its incidence is rising compared with other head and neck sites (especially in the 20–44-year age group). In addition, the tongue is the only oral site with tumours of different aetiologies, that is, both HPV-associated in the posterior third (base tongue carcinoma) and non-HPV-associated in the anterior two-thirds (oral or mobile tongue carcinoma)[2]. Mobile tongue carcinoma is associated with poorer survival and a lower rate of local tumour control than other sites of head and neck cancer[3], and the survival rate (~50%) has remained almost unchanged in the past four decades[2].

In addition to the genetic changes in the epithelium, the tumour microenvironment in mobile tongue cancer has a decisive role in the poor prognosis of the affected individuals, probably because of site-specific properties that represent molecular crosstalk between cancer cells and the tumour microenvironment[3,4]. The tumour microenvironment is comprised of a complex network of extracellular matrix components and cells, including cancer-associated fibroblasts (CAFs)[5]. CAFs that have a myofibroblastic phenotype were shown to be associated with mobile tongue carcinogenesis in both a rat model[6] and in human patients[7]. In patients with mobile tongue carcinoma, recurrence and disease-specific survival are strongly associated with an increased frequency of CAFs[8,9]. Furthermore, the tumour microenvironment of both metastatic regional lymph nodes and matched primary tongue tumours host CAFs, suggesting that CAFs not only promote tumour invasion but also facilitate metastasis[10].

These clinicopathological findings are supported at the molecular level by invasion assays that use an organotypic model of myoma (obtained from routine surgical specimens of human uterus leiomyomas), which approximates *in vitro* the natural tumour microenvironment in both the variety of the cellular components (such as, endothelial cells, smooth muscle cells, lymphocytes, macrophages, fibroblasts and myofibroblasts) and the presence of various extracellular matrix proteins and glycoproteins (such as collagen types I, II and III, and laminins)[11]. Human HSC-3 tongue cancer cells cultured in the myoma model showed increased invasiveness and enhanced collagen degradation compared with the traditional collagen organotypic culture[11]. Recently, Webber and colleagues used a panel of five different cancer cell lines and showed that cancer cells transmit information to stromal fibroblasts using exosomes that possess membranous transforming growth factor-β (TGFβ), which induces transdifferentiation of stromal fibroblasts into myofibroblasts or CAFs[12]. In addition, cancer cells can also recruit resident and bone marrow-derived mesenchymal stem cells (precursors of CAFs)[13]. Collectively, it becomes evident that the development, progression and spread of mobile tongue cancer, similar to breast, gastric, colon and hepatocellular carcinomas, not only depends on the genetic characteristics of the tumour cells, but also on the molecular interactions with its microenvironment[4].

Current anticancer modalities usually target only the malignant cells of the tongue. Targeting both the tumour cells and the tumour microenvironment, however, seems to hold new hope for the patients, and several preclinical studies[14] and Phase I–III clinical trials on this line of research are already underway. This includes agents that interfere with CAF differentiation (such as sibrotozumab), cytokine inhibitors (such as bryostatin-5) and others[4,15].

Marilena Vered and Dan Dayan are at The Maurice and Gabriela Goldschleger School of Dental Medicine, Tel-Aviv University, Tel Aviv 69978, Israel.

Marilena Vered is also at the Institute of Pathology, The Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel.

Tuula Salo is at the Department of Diagnostics and Oral Medicine, Institute of Dentistry, University of Oulu, Oulu FI-90014, Finland.

Correspondence to M.V.
e-mail: mvered@post.tau.ac.il
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Competing interests statement
The authors declare no competing financial interests.