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Application of digital pathology to evaluate potential cancer-associated fibroblast biomarkers in head and neck cancer patients.

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Introduction: Head and neck cancers (HNC) are a diverse group of aggressive malignancies with high morbidity and mortality, mainly due to late diagnosis, limited treatment options and tumor recurrence. Tumors are highly complex and heterogeneous structures in which growth and dissemination is not only governed by the cancer cells intrinsic mechanisms, but also by the surrounding tumor microenvironment (TME). Cancer-associated fibroblasts (CAFs) emerge as predominant TME components and key players in the generation of permissive conditions that ultimately impact in tumor progression, metastatic dissemination and treatment response. To date, diverse markers have been reported and used to characterize functionally the different CAF subpopulations, thereby revealing their heterogeneity and functional diversity. Therefore, a better understanding of the molecular processes governing the transformation of stromal fibroblasts into CAFs and their spatial distribution in tumors is crucial to improve current diagnostic and prognostic tools as well as to develop more personalized treatment strategies targeting the TME, including CAF-based therapies.

Objective: This is an exploratory study to evaluate the expression of various CAF biomarkers, previously reported in the literature, in a set of paired tumor and normal tissues from HNC patients.

Material and method: FAP, ?SMA, FN1 and CDH6 expression was evaluated by immunochemistry (IHC) in 8 paired tumor and normal tissues samples (vestibular fold) from surgically-treated HNC patients. IHC quantitative analysis was accomplished using QuPath software performing positive cell detection and training to discriminate between the epithelial and stromal compartments.

Results and discussion: FAP protein expression was predominantly detected in the tumors, while being absent in patient-matched normal samples. Moreover, the number of positive cells detected in the tumor stromal compartment was much higher than in the epithelial compartment. These data support FAP as a bona fide CAF biomarker in HNC. By contrast, FN1 protein expression was preferentially detected in the stromal compartment, without differences between tumor and normal samples. Therefore, FN1 appears to be a good fibroblast marker in HNC, although unable to distinguish between normal fibroblasts (NFs) and CAFs. Regarding ?SMA protein, its expression was only detected in blood vessels and muscle fibers. Surprisingly, ?SMA staining was undetectable in stromal fibroblasts. According to these results, ?SMA does not seem to be a reliable CAF biomarker in the context of HNC. For CDH6 protein, its expression was more abundant in the epithelial compartment, although without differences between paired normal and tumor samples. These data show that CDH6 expression is not a useful

biomarker to identify CAFs in HNC.

Conclusion: Our findings clearly demonstrate FAP as a specific biomarker to identify CAFs in HNC, but not FN1, ?SMA and CDH6.