Upregulation of apoptosis related genes in clinically normal tongue contralateral to squamous cell carcinoma of the oral tongue - an effort to maintain tissue homeostasis

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ABSTRACT

Background & Purpose:

The field cancerization concept indicates the presence of pre-cancerous changes in clinically normal tissue surrounding the tumor. In squamous cell carcinoma of the oral tongue (SCCOT) which is infrequently linked to human papillomavirus infection, we have previously reported that clinically normal tongue contralateral to tumor (NTCT) is molecularly abnormal. Here, combining our transcriptomic and genomic data, we aimed to investigate the contribution of molecular changes in NTCT to cancer development.

Materials & Methods:

Microarray gene expression data of 14 healthy controls, 23 NTCT and 29 SCCOT samples were investigated to characterize transcriptional profiles in NTCT. Whole exome sequencing and RNA-sequencing data of paired NTCT and tumor samples from 15 SCCOT patients were used to study correlation between copy number variation and differential gene expression.

Results:

Partial least squares discriminant analysis identified 61 mRNAs that distinguish NTCT from healthy tongue. Functional enrichment analysis of the 22 upregulated genes showed increased “positive regulation of nitrogen compound metabolic process” in NTCT. All 12 genes involved in this process have roles in apoptosis (anti- and/or pro-apoptotic). Compared to healthy controls, Zinc Finger Protein 395 (ZNF395), a pro-apoptotic tumor suppressor located on chromosome 8p, was the only gene showing increased mRNA level in NTCT whereas decreased in SCCOT.

Conclusion:

NTCT is susceptible to malignant transformation, where tissue homeostasis is maintained at least partly through regulation of apoptosis. Loss of the pro-apoptotic gene ZNF395 could thus initiate cancer development.

Keywords: SCCOT; field cancerization; etiologic field effect; apoptosis; ZNF395