

SIRNA SCREEN OF UPREGULATED GENES IDENTIFIES TARGETS FOR A MULTIAANTIGEN POLYPEPTIDE VACCINE TO PREVENT HNSCC

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Background Oral Dysplasia (OD) is a precursor lesion for developing head and neck squamous cell carcinoma (HNSCC). The risk of developing HNSCC from OD is 12% in 2 years. In HNSCC, presence of tumor-specific type I T-cells predict improved progression free survival compared to the patients with tumor that do not have tumor-specific Th1 T-cells. We therefore sought to identify candidate antigens overexpressed in both OD and HNSCC as targets for a vaccine that can both treat and prevent HNSCC.

Methods Selected target genes were overexpressed in human OD and HNSCC and were selected from curated open access GEO data sets. Functionally relevant candidate genes were selected as targets that were necessary for survival using high-throughput siRNA screen. We evaluated the effect of 3 pooled siRNA per target in 3 human HPV negative HNSCC cell lines (FaDu, SSC15, SCC25) and 1 hyperplastic keratinocyte (NOK) as compared to the non-malignant human gingival fibroblast (HGF) cell line. We prioritized candidate antigens whose loss induced $\geq 50\%$ decreased viability in HNSCC cell lines and OD but not in non-malignant gingival cell line.

Results We identified 46 targets that were overexpressed greater than 2-fold in both OD and HNSCC but not in normal tissue, from 2 OD and 5 HNSCC datasets including 206 normal samples, 66 OD samples, and 198 HNSCC samples. To increase the number of candidate antigens, a literature search of gene expression studies, not included in public data set was performed including four studies with 58 normal samples, 21 OD samples, 179 HNSCC. 80 genes that were highly overexpressed in OD and HNSCC and overexpressed in greater than 75% of datasets were selected for the siRNA screen. 17 candidate antigens that reduced viability $>50\%$ in 2 or more HNSCC cell lines were selected: COL1A1, COL1A2, COL4A1, LOXL2, JUP, WDR66, POSTN, TNC, HOXB7, WDR72, TENM3, FN1, PDPN, SERPINE1, INDO, IFI6, ACTN1. All these 17 genes have known roles in HNSCC tumor progression.

Conclusions We have identified 17 candidate antigens that are functionally relevant to survival in OD and HNSCC. Future studies will evaluate if these candidate antigens are immunogenic in OD and HNSCC by evaluation if autoantibodies to these targets are present in the serum of OD and HNSCC patients but not in normal controls. These antigens will be used to design an MHC class II multiantigen polyepitope vaccine.

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