Molecular characterization of squamous cell carcinoma of the anal canal (SCCA)


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Abstract #176039

Background: Nivolumab has shown promising results in SCCA patients. The majority of SCCA cases have been linked to prior human papillomavirus (HPV) infection. However, HPV negative tumors are frequently TP53 mutated and often resistant to therapy. Molecular characteristics of SCCA are largely undefined. Here we explored the underlying biology of SCCA and the differences between TP53 wild-type (TP53-WT) and TP53-mutated (TP53-MT) tumors.

Methods: SCCA specimens underwent multiplex testing with protein expression (HIC), gene amplification (ISH), and sequencing (NGS). Tumor mutational burden (TMB) was calculated using only somatic non synonymous missense mutations. Chi-square tests were used for comparative analyses.

Results: In total, 253 tumors were studied. The most frequently mutated genes included PIK3CA (24%), ARCA2 (14%), FBXW7 (12.4%), TP53 (9.7%), and PTFN (8.9%). In a subset of 23 tumors subjected to Illumina NextSeq (592 genes) testing, the most common mutations were NOTCH2 (30%), NOTCH1 (27.3%), PDGF (21.7%), TC52 (17.4%), PTEN (14.3%), BRCA1 (13.6%), ARCA2 (13.0%), PIK3CA (13.0%), and FBXW7 (9.5%). Tumors frequently expressed MRP1 (97.6%), EGFR (92.7%), TOP2A (88.5%), TOPO1 (69.5%), BRCA2 (59.2%), and NOTCH1 (592 gene) testing, the most common mutations were TP53-MT and TP53-WT tumors and for correlation of TMB to PD-1 and PD-L1 status.

Conclusions: Molecular differences between TP53-MT and TP53-WT SCCA indicate different carcinogenic pathways and underlying tumor biology. The higher incidence of BRAF and RB1 mutations in TP53-MT tumors compared to TP53-WT may reflect different oncogenic signaling pathways and a potential role for BRAF inhibition. The higher rate of ERCC1 expression in primary SCCA may indicate that platinum resistance is more common in primary tumors than metastatic tumors. PD-1 and PD-L1 expression were seen in both TP53-MT and TP53-WT tumors, suggesting TP53 mutation status is not predictive of response to immune checkpoint inhibition. Frequent mutations in the NOTCH signaling pathway suggest a potential drug target in SCCA using NOTCH inhibitors. Low frequency of EGFR and HER2 gene amplifications suggest potential drug targets (e.g. trastuzumab) in select SCCA patients.

References

Figure 1. Comparison of primary (blue, N = 69) and metastatic (red, N = 110) SCCA. Primary and metastatic lesions were from unpaired samples. Statistically significant differences were found in FN1 and TOP2A expression (arrows indicate P < 0.05). A comparison of NGS biomarkers revealed no statistically significant differences.

Figure 2. Comparison of IHC expression for PD-L1 (SP142) 26.5% (9/34) in TP53-MT and 1.1% (1/93) in TP53-WT tumors. The difference in expression was statistically significant (P = 0.001).

Figure 3. Comparison of primary (blue, N = 69) and metastatic (red, N = 110) SCCA. Primary and metastatic lesions were from unpaired samples. Statistically significant differences were found in FN1 and TOP2A expression (arrows indicate P < 0.05). A comparison of NGS biomarkers revealed no statistically significant differences.