Head and neck cancer recurrence following radiation associated w high tumor PD-L1 expression

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Recurrence of head and neck squamous cell carcinoma (HNSCC) negative for human papillomavirus (HPV) following radiation therapy was associated with high tumor levels of the protein PD-L1.

The study is published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research, by Heath D. Skinner, MD, PhD, assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, Houston.

According to Skinner, infection with certain types of HPV can cause some cases of HNSCC, but many cases are HPV-negative and patients with this form of the disease have particularly poor outcomes following treatment.

He also explained that radiation forms the backbone of curative treatment of HPV-negative HNSCC but that 30 to 50 percent of patients go on to have local disease recurrence and ultimately die from their disease following this treatment.

In this study, Skinner and his colleagues focused on identifying and validating potentially targetable biomarkers to potentially improve survival for patients with HPV-negative HNSCC.

The researchers started by identifying proteins whose levels were

increased in an HPV-negative HNSCC cell line made resistant to radiation compared with the original cell line. Among the proteins whose levels increased the most were PD-L1, AXL, and PI3K pathway proteins.

Further analysis of additional HPV-negative HNSCC cell lines showed that PD-L1 levels correlated with AXL and PI3K signaling. In addition, inhibition of either AXL or PI3K using two different methods decreased PD-L1 levels.

The in vitro observation that PD-L1 levels correlated with AXL and PI3K signaling was confirmed in samples from two cohorts of 68 and 97 patients with locally advanced HPV-negative HNSCC, respectively, as well as in The Cancer Genome Atlas HPV-negative HNSCC cohort.

In univariate analysis using three different methods to analyze PD-L1 levels in three different cohorts, three-year loco-regional recurrence rates were 60 percent, 70 percent, and 50 percent for tumors with high levels of PD-L1 compared with 20 percent, 25 percent, and 20 percent for tumors with low levels of PD-L1. The association between PD-L1 levels and loco-regional recurrence of disease remained statistically significant in multivariate analysis.

"My research focus is identifying and validating biomarkers of tumor radioresistance that can be targeted therapeutically," said Skinner. "We were excited to identify and validate PD-L1 as a biomarker of poor outcomes following radiation for patients with HPV-negative HNSCC. Because there are multiple immunotherapeutics that target the PD-1/PD-L1 pathway, our data suggest that combining radiation and a PD-1 or PD-L1 inhibitor could improve outcomes for these patients.

"We were surprised by the magnitude of the difference in outcomes between patients with high and low PD-L1 levels," he added. "However,

we saw very consistent results using several different patient cohorts and using different methods of PD-L1 analysis so we are confident that this is a clinically relevant observation."

Skinner explained that because the main limitation of the study is that the clinical data for the association between AXL and PI3K and PD-L1 are correlative in nature, the researchers are currently investigating the specific contexts in which modulating and/or targeting AXL and PI3K lead to alterations in PD-L1 expression and, ultimately, improved response to radiation.

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