Investigating the Role of CXCR2 in Head and Neck Cancer

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Introduction: Head and neck cancer (HNC) is the seventh most common cancer globally, with 90% of HNC comprised of Head and Neck Squamous Cell Carcinoma (HNSCC). Despite significant improvements in anticancer therapies, long-term survival rates for patients with advanced-stage HNSCC have not significantly increased in the past 30 years. Although the field of immunotherapy has primarily focused on the adaptive immune response, accumulating evidence suggests that Natural Killer (NK) cells are also important. Interestingly, we discovered that inhibition of the CXCL1/CXCR2 cytokine signaling pathway increased both the number and activity/cytotoxicity of NK cells. Activation of CXCL1/CXCR2 has been implicated as a negative prognostic factor in many cancers, including HNSCC. Our laboratory has new evidence that the CXCL1/CXCR2 cytokine signaling pathway inhibits antitumor functions of NK cells, thereby promoting immune resistance and tumor growth. Here we demonstrate the effect of CXCR2 inhibition on HNSCC tumor growth and immune cells using an *in vivo* mouse model.

Methods: Mouse oral head and neck cancer cells (MOC-1) were cultured and injected into the buccal region of C57BL/6 mice and allowed to grow for 3 weeks. Once the tumors reached 100mm^3, treatment with Vehicle, 10mg/kg SB225002 (CXCR2 inhibitor), 1ug/kg CXCLI1, or combination SB225002+CXCL1 was started. Treatments were administered by IP injection 3 times per week for 3 weeks. Tumor measurements and mouse weights were measured 3 times per week throughout the experiment. After 3 weeks of treatment, mice were sacrificed and peripheral blood, tumors, and draining lymph nodes were harvested. Blood was used to assess cytokine response by ELISA and immune cell characterization by flow cytometry. Tumor sections were analyzed by immunofluorescence to determine immune cell infilitration. Mixed model statistics were used to assess differences in the rate of tumor growth between groups over time. ANOVA was used to assess differences in tumor volumes between groups at the time of sacrifice. P values less 0.05 were considered significant.

Results: Mice treated with SB225002 along exhibited a reduction in tumor volume when compared with mice in the vehicle, CXCL1, and combination groups. Interestingly, the mice treated with SB225002 + CXCL1 showed a rebound effect in tumor growth, with no difference between the combination treatment and the vehicle and CXCL1 groups. There were no significant differences in mouse weight throughout the study. Additional results are pending additional research/data collection.

Conclusions: Inhibiting CXCR2 decreased tumor volume in mice. Interestingly, a rebound effect was seen when mice were treated with CXCL1 in addition to SB225002, suggesting that the effects of SB225002 can be overcome with an increased concentration of CXCL1. It is unclear if the inhibition of growth by SB225002 was due to direct tumor effects, or indirect immune cell activation. Studies are ongoing.

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