ASTRO 2025 Abstract Draft

Title: Interrogating contributions of the sensory neuroimmune axis to treatment resistance in head and neck squamous cell carcinoma

Purpose/Objectives In patients with oral squamous cell carcinoma, high levels of intratumoral expression of a sensory neuropeptide, CGRP, has been correlated with reduced survival. There is limited mechanistic understanding of how sensory neural involvement in head and neck squamous cell carcinoma (HNSCC) affects treatment resistance with radiation and immunotherapy. The objective of this work was to examine the effect of sensory neuropeptides (CGRP and Substance P) on immune cells in the tumor microenvironment (TME) and delineate their contribution to treatment resistance in models of HPV-negative HNSCC. We hypothesized that CGRP promotes regulatory T cell (Treg) and impairs effector T cell (Teff) infiltration in the TME.

Materials/Methods

Orthotopic murine models of HPV- HNSCC were established via implantation of 1.0×10^5 MOC2 cells into the buccal mucosa of age-matched control, CGRP knockout, or Substance P knockout mice. Tumor growth was monitored 2-3 times weekly through caliper measurements and tumor volume was calculated. When tumor volume was > 150 mm^3, unimodal or multimodal treatment with radiation/RT (8Gy x 3) and/or immunotherapy/IO (weekly intraperitoneal injection of anti-PD1 therapy) was initiated. Flow cytometry was performed on blood, draining lymph nodes and whole tumors to assess infiltration, activation status, and survival of the full immune landscape in control and neuropeptide knockout mice.

Results

Mouse models with genetic knockout (KO) of substance P or CGRP have greater treatment response to radiation therapy (8Gy x 3), when compared to control mice. When paired with anti-PD1 therapy, improved survival was observed as noted by hazard ratios of 0.233 with Substance P KO and 0.078 with CGRP KO. Of note, 84% of CGRP KO mice treated with RT+IO exhibited tumor eradication, with a cure rate of 83% upon subsequent rechallenge. Flow cytometry analysis revealed a significant increase in effector T cell infiltration in the TME and an associated increase in CD8:Treg ratio in the TME of CGRP KO mice treated with RT.

Conclusions

The sensory neuropeptide CGRP, a key component of neuroinflammation, impairs treatment response to radiotherapy by reducing infiltration of Teff cells in the tumor. Radiotherapy paired with anti-PD1 therapy in CGRP KO mice favors an antitumor immune TME by reducing immunosuppressive Tregs; contributing to a high frequency of tumor eradication and cure following treatment. These studies reveal that CGRP may be a valuable target to improve therapeutic response to radioimmunotherapy in HNSCC.