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

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Introduction

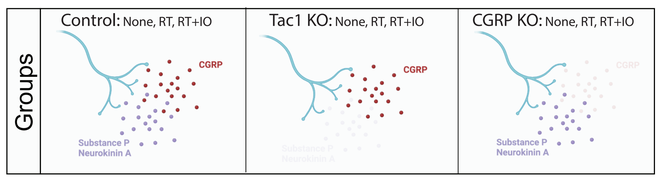
High levels of intratumoral expression of a sensory neuropeptide, CGRP, has been correlated with reduced survival in head and neck squamous cell carcinoma (HNSCC). There is limited mechanistic understanding of how sensory neural involvement affects treatment resistance with radiation and immunotherapy

Objective: Examine the effect of sensory neuropeptides on immune cells in the tumor microenvironment (TME) and delineate their contribution to treatment resistance in HNSCC

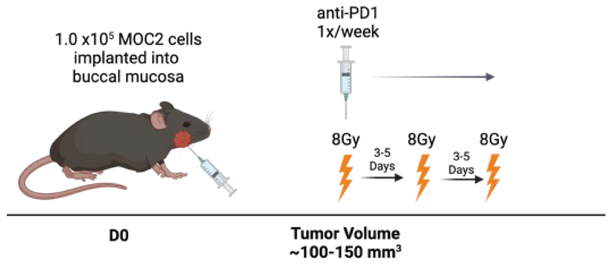
Hypothesis: CGRP promotes regulatory T cell (Treg) and impairs effector T cell (Teff) infiltration in the TME

Methods

Animal Models:



Treatment Paradigm:



Treatment Response Metrics:

- Tumor Volume
- Overall Survival
- TME immunophenotyping via flow cytometry

Results

CGRP KO improves treatment response and survival

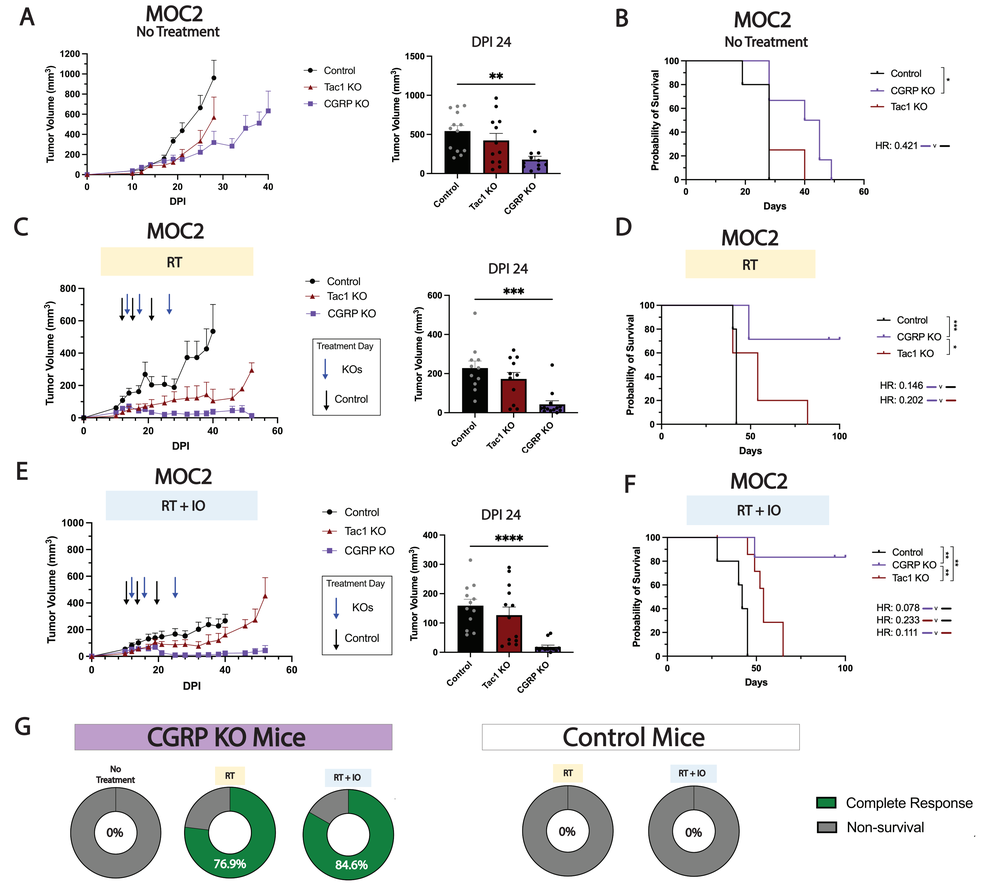


Fig 1: (A) Tumor growth curves for untreated mice and **(B)** the associated Kaplan-Meier survival curve. **(C)** Tumor growth curves for mice treated with RT alone (8Gyx3) and **(D)** the associated Kaplan-Meier survival curve. **(E)** Tumor growth curves for mice treated with combination RT+IO (8Gyx3 and weekly anti-PD1) and **(F)** the associated Kaplan-Meier survival curve. **(G)** CGRP KO mice treated with RT have high rates of complete response, which is not observed in WT control mice. Statistical analysis of tumor volumes was conducted using ordinary one-way ANOVA with Holm-Sidak correction for multiple comparison. n = 5-7 mice per treatment group.

CGRP KO improves antitumor immunity in TME

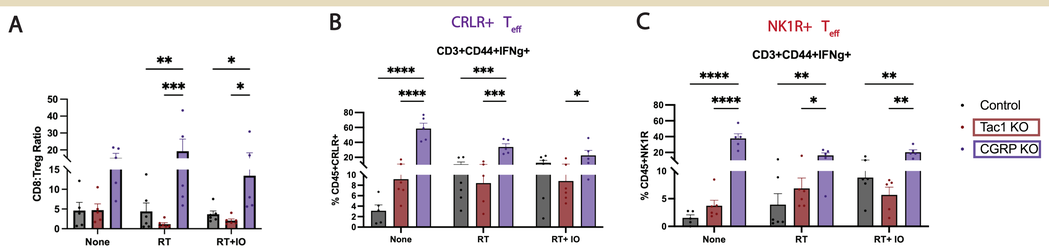


Fig 2: (A) CD8:Treg ratio is increased in CGRP KO mice treated with RT and RT+IO. **(B)** Frequency of CRLR+ Teff cells and **(C)** NK1R+ Teff cells increases in CGRP KO. Analysis was conducted using two-way ANOVA with Holm-Sidak correction for multiple comparison. n = 5 per group.

Conclusions

CGRP 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; contributing to a high frequency of tumor eradication.

These studies reveal that CGRP may be a valuable target to improve therapeutic response to radiation and immunotherapy in HNSCC

References

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