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Semaphorin 4D produced by human head and neck squamous cell carcinoma induces myeloid derived suppressor cells expansion from peripheral blood monocytes

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Background

Immune suppression is one of the hallmarks by which head and neck squamous cell carcinoma (HNSCC) develops a tumor permissible environment[1]. Semaphorin 4D (Sema4D), known for its various developmental, physiological and pathological effects, was recently shown to play a role in regulating the immune system[2]. Sema4D is expressed in many epithelial tumors including HNSCC[3]; yet, the effect of Sema4D on modulating the inflammatory profile within the tumor microenvironment of HNSCC remains to be elucidated.

Methods

Human HNSCC cell lines HN6 and HN13 were used to study the effect of Sema4D produced in tumor conditioned media (TCM), on myeloid and T cells separated from human peripheral blood mononuclear cells (PBMC) of healthy donors. Neutralizing anti-Sema4D antibody and Sema4D immune depletion from the TCM were carried out. Lentivirus shRNA was also used to knock down Sema4D in HNSCC-HN6 cells.

Results

Treatment of PBMC with TCM from HNSCC HN6 and HN13 cell lines resulted in a significant induction in myeloid derived suppressor cells (MDSC; $CD33^+$ $CD11b^+$ $HLA\text{-}DR^{-/low}$) from freshly isolated $CD33^+$ cells. This increase in MDSC corresponded with the suppression of autologous T cell proliferation and a reduction in IFN-γ production. Blockade of Sema4D in the TCM of HN6 and HN13 using anti-Sema4D antibody resulted in a significant reduction in the MDSC population. Furthermore, TCM from HN6 Sema4D-shRNA rescued the MDSC-mediated T cell suppression and recovered IFN-γ, compared to the control. Analysis of the recovered T cell population showed an increase in the effector T cell population ($CD4^+Tbet^+$ and $CD8^+Tbet^+$), and a decrease in regulatory T cells ($CD4^+CD25^+FoxP3^+$). Mechanistically, we found a decrease in arginase-1 produced by myeloid cells cultured in HN6 Sema4D-shRNA TCM, as well as a reduction in the immune suppressive cytokines, TGF-β, and IL-10.

Conclusion

This study describes a novel immunosuppressive mechanism for HNSCC through Sema4D induction of MDSCs. Collectively; our work highlights the therapeutic potential of Sema4D inhibition as a strategy to improve the efficacy of immunotherapy in HNSCC.

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