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A Method for Monitoring Cancer and for Regulation of Semaphorin 4D to Improve Cancer Immunotherapy Regimens

Summary

The efficacy of current cancer immunotherapies has been limited by the response of immunosuppressive elements such as myeloid derived suppressor cells (MDSC) and T regulatory cells. Understanding the mechanism behind the suppression of antitumor immunity, and finding ways to revert it, should lead to improved cancer immunotherapy outcomes. Tumor cells overexpress several cytokines to manipulate their microenvironment, among which are multiple Semaphorins. Semaphorin 4D (Sema4D) is one such pro-angiogenic cytokine, and it is implicated in the regulation of the immune system. **Researchers at UMB have discovered the role of Sema4D produced by head and neck squamous cell carcinoma (HNSCC) in the development of immunosuppression in the tumor microenvironment.** Sema4D was found to be involved in the induction of MDSC, and therefore T-cell suppression. Knock-down of Sema4D blocks MDSC induction and recovers effector T-cells. This novel mechanism and its targeted inhibition can recover an anti-tumorigenic inflammatory profile. This work suggests the use of Sema4D as a therapeutic target for improving the efficacy of cancer immunotherapy regimens.

Key Investigator

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Field

Immunology
Oncology

Technology

Target underlying the suppression of antitumor immunity

Advantages

Addresses the problem of immunosuppression in the tumor microenvironment, which is known to limit the efficacy of cancer immunotherapies

Tractable druggable target with potential to improve cancer immunotherapy

Status

Available for licensing

UMB Docket Reference

RY-2015-129

External Reference

Younis RH et al. (2016) *J Immunol*. 196(3):1419-1429.

Derakhshandeh R et al. (2018) *Oncotarget*. 9(13) 11126-11144.

Market

HNSCC is the sixth most common malignancy worldwide. Most patients present locally advanced disease and receive multimodality treatment, including immunotherapy. However, HNSCC induces an immunosuppressive state that remains as long as two years following treatment with curative intent. This result contributes to the 5-year progression-free survival rate of ~50%. To date, Erbitux®, Keytruda®, and Opdivo® are the only immunotherapies approved for the treatment of HNSCC in the US, with Opdivo® recently showing improved survival in treatment-refractory patients. As immunotherapies become the treatment of choice, both as first and second-line treatments, Sema4D modulation could be used in the majority of HNSCC patients, which are approximately 61,760 per year and account for 3%-5% of all cancers in the US.

Technology

This technology refers to a method of treating HNSCC by targeting Sema4D and its use to manipulate antitumor immunity. Based on *in vitro* work on HNSCC cell lines, including Sema4D knockdown experiments, Sema4D was found to immunosuppress the tumor microenvironment. The key findings that illustrate the role of Sema4D as a novel target for modulating immunosuppression are:

1. Sema4D produced by HNSCC increased the number of MDSC, promoted their viability, and increased the production of suppressive cytokines by MDSC, resulting in suppression of T-cells.
2. Knockdown of Sema4D in an HNSCC cell line led to a loss of MDSC function.
3. Co-culture of myeloid and T cells in conditioned medium of HNSCC cells with Sema4D knockdown restores an anti-tumor inflammatory profile.

Together, this work describes a novel immunosuppressive role for Sema4D in HNSCC and highlights it as a therapeutic target for enhancing the antitumorigenic inflammatory response in HNSCC and other malignancies.

Technology Status

This technology has been tested in HNSCC cell lines.

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