TECHNOLOGY

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

OVERVIEW

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.

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 the 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.

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CATEGORIES

- Diagnostics
- Biomarker
- Therapeutics

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ATTACHMENTS

- Download RY-2015-129 SRC Summary 05_14_2018.pdf

EXTERNAL RESOURCES

- Younis RH et al. (2016) J Immunol. 196(3):1419-1429.
- Derakhshandeh R et al. (2018) Oncotarget. 9(13) 11126-11144.

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