

Sulforaphane Modulates Glioma-mediated Myeloid-derived Suppressor Cell Development

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Introduction

Glioblastoma (GBM) is the most common primary tumor of the brain and has terrible long term survival. The local and systemic immunosuppressive environment created by GBM allows it to evade immunosurveillance. Myeloid-derived suppressor cells (MDSCs) are a critical component of this immunosuppression. Understanding mechanisms of MDSC formation and function are key to developing effective immunotherapies.

Methods

In this study, we developed a novel model to reliably generate human MDSCs from healthy-donor CD14+ monocytes by culture in human glioma-conditioned media (GCM). Monocytic MDSC (CD14+/- HLA-DR-) frequency was assessed by flow cytometry and confocal microscopy. The resulting MDSCs robustly inhibited T cell proliferation. A cytokine array identified multiple components of the GCM potentially contributing to MDSC generation, including Monocyte Chemoattractive Protein-1 (MCP-1), IL-6, IL-8, and Macrophage Migration Inhibitory Factor (MIF).

Results

Of the identified cytokines, MIF is a particularly attractive therapeutic target as a naturally occurring MIF inhibitor (Sulforaphane; SFN) derived from broccoli sprouts has excellent oral bioavailability. SFN inhibits the transformation of normal monocytes to MDSCs by GCM in vitro at pharmacologically relevant concentrations that are non-toxic to normal leukocytes. This is associated with a corresponding increase in mature dendritic cells. SFN treatment had similar pro-inflammatory effects on normal monocytes in fresh media but specifically increased immature dendritic cells.

Conclusions

Thus, we have used a simple in vitro model system to identify a novel contributor to GBM immunosuppression for which a natural inhibitor exists. Further study will be required to determine if this can potentiate GBM immunotherapy in vivo.

Learning Objectives

By the conclusion of this session, participants should be able to:

- 1) Describe the importance of myeloid derived suppressor cells in GBM induced immunosuppression
- 2) Discuss the role of MIF in MDSC development
- 3) Identify sulforaphane as an effective inhibitor of MDSC development in-vitro

References