Cholinergic Modulation of Tumor-Associated Macrophages for the Treatment of Glioblastoma

Kevin Kwan MD; Camila Gonzalez; Tia Turner; Julia Rachel Schneider BS; John A. Boockvar MD; Rosamaria Ruggieri PhD; Marc H. Symons PhD

Department of Neurosurgery, Zucker School of Medicine at Northwell / Hofstra School of Medicine

CNS 2018 ANNUAL MEETING HOUSTON, TEXAS OCTOBER 6-10, 2018

Introduction

Glioblastoma multiforme (GBM) remains the most aggressive brain tumor with a 5-year overall survival rate of less than 4%. Tumor-associated macrophages (TAMs) have been shown to play a critical role in GBM invasion and radiotherapy resistance. Activation of the cholinergic nervous system has previously been shown to inhibit inflammation through stimulation of the 7 nicotinic acetylcholine receptor (a7nAChR) on macrophages. Thus we sought to investigate the effects of cholinergic modulation on GBM-associated TAMS in an in vitro and in vivo model.

Methods

In vitro microglia-stimulated glioblastoma cell invasion was quantified using a three-dimensional Matrigel transwell invasion assay of murine GL261 glioblastoma cells in co-culture with primary microglia. Cholinergic modulation of the malignant behavior of glioblastoma in vivo was studied using the C57Bl/6-GL261 syngeneic orthotopic model. In vivo invasion was determined by quantifying the number of Ki-67-stained invading cells, normalized to tumor circumference.

Results

We showed that GTS-21, a selective partial agonist of a7nAChR, completely inhibits microglia-stimulated glioblastoma cell invasion in vitro. GTS-21 does not affect serum-stimulated glioblastoma cell invasion, indicating that GTS-21 inhibits microglia, rather than tumor cells. Intraperitoneal administration of the blood-brain barrier permeable acetylcholinesterase inhibitor galantamine (8 mg/kg) decreased tumor invasion by 58% (p=0.05).

Learning Objectives

1) Describe the importance of tumor-associated macrophages in the pathophysiology of Glioblastoma.

2) Discuss, in small groups, the potential pathway through which cholinergic stimulation can be utilized for the treatment of cerebral neoplasms.

3) Identify an effective treatment strategy for the treatment of glioblastoma through cholinergic stimulation.

Conclusions

These results suggest that cholinergic modulation may be useful as a novel therapeutic modality for the treatment of GBM via inhibition of TAMs. We anticipate that the effect of galantamine would be optimal in the context of chemo-radiation, to which TAMs are known to provide resistance. Galantamine is already FDA-approved for the treatment of Alzheimer's Disease, thereby accelerating the transition of this treatment modality from bench to bedside.