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

Paramagnetic Nanoparticles Conjugated with Lipopolysaccharide for Blood-Brain Barrier Disruption in a Murine Model of Glioblastoma

Andrew Joshua Kobets MD, MHS; Muhammad Babar Khan MD; Mahantesh Navati PhD; Kevin Kwan MD; Yao Liu MD; Jonathan P Nakhla MD; Joel Friedman MD, PhD; John A. Boockvar MD; Rosamaria Ruggieri PhD; Marc H. Symons PhD

Feinstein Institute for Medical Research/Northwell Health, Manhasset, NY

Introduction

Glioblastoma (GBM) is the most aggressive primary adult brain tumor with only 14.6 months median survival. Carrier nanoparticles have emerged as a novel strategy for chemotherapeutic delivery, yet penetration of the blood-brain barrier (BBB) and tumor retention remain significant hurdles. The evolution of paramagnetic nanoparticles (PMNPs) shows promise for reliable, magnetically-targeted drug delivery, and coupled with a lipopolysaccharide-coating (LPS-PMNPs) allows for concurrent, BBB disruption.

Methods

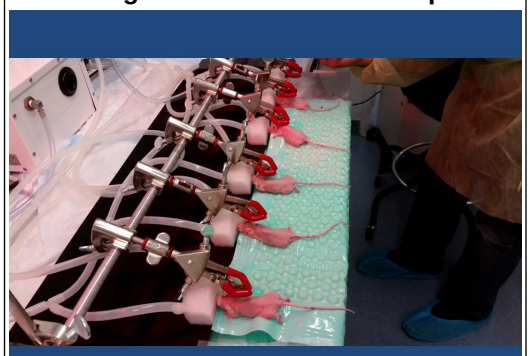
Luciferase-expressing GBM6 cells were implanted intracranially in nu/nu immunodeficient mice to model GBM in two experiments. First, bioluminescence assays (BLIs) characterized tumor growth postoperatively in cohorts administered LPS-PMNPs, inert PNMPs (OA-PMNP), or saline intravenously at four weeks. Magnets were positioned external to the tumor for one hour post-injection. Subsequent BLIs trended tumor growth with survival. The second experiment involved LPS-PMNPs, OA-PMNPs, or saline injection postoperatively, followed by magnetic localization. Afterwards, Evans blue dye (EBD) was administered as an albumin-bound marker of BBB breakdown. The mice were perfused, the tumors homogenized, and the dye extracted for spectrophotometry.

Results

Tumor size doubled every 5.8 days, and mice expired at a mean 52 days. LPS-PMNPs reduced BLI signal three

This effect was reversed six days post-injection (p=0.39). EBD was significantly extravasated in LPS-PMNP -treated tumors compared to all other tumors (p=.011). No immediate particle-associated adverse reactions occurred and survival was similar between all groups (p=0.27) with a trend toward survival between the LPS group and highest-dose PMNP group (53.5 vs. 47.8 days, p=0.12).

Magnetic Localization Setup

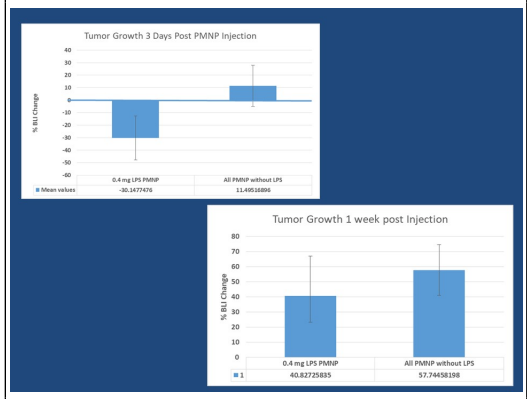


Anesthetized mice were placed under cone magnets localized over tumor implantation sites after particles or saline were injected intravenously.

Conclusions

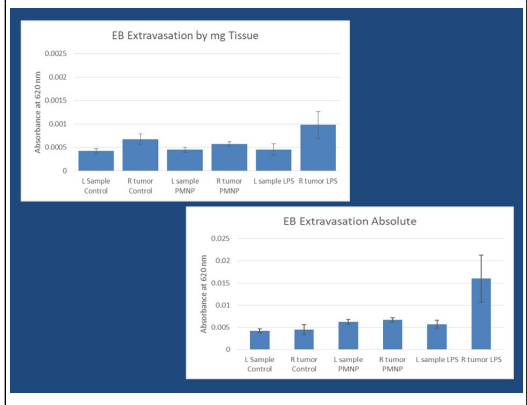
The BBB can be safely and reversibly disrupted for targeted permeability of large molecules in a GBM model. LPS induces transient disruption of bioluminescence of tumors and increases tumor absorption of albumin -bound EBD. Future work will start with packaging known chemotherapeutics not normally BBB permeable in LPS-PMNPs to determine delivery efficacy and anti-neoplastic effects on survival.

BLI Data 2



BLI data for LPS-PMNP and OA-PMNP injected groups at 3 days and 1 week

EBD Data

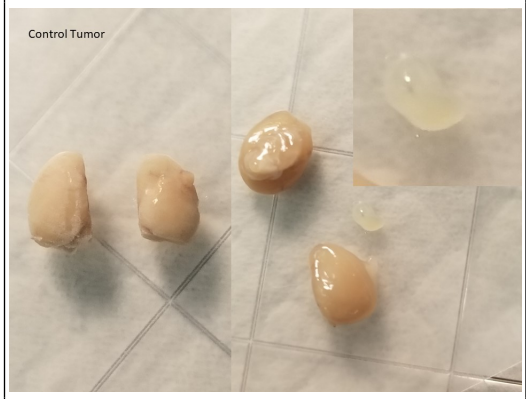


Increased Evans blue dye extravasation in tumors injected with LPS-PMNPs

Learning Objectives

1) Describe the importance of BBB breakdown for the delivery of therapeutics in GBM 2) Discuss strategies for therapeutic penetration in GBM and mechanisms for LPS effects on tumor and endothelium, 3) Identify an effective treatment for BBB impermeability and strategize possible GBM treatments in the future.

Control Mouse Tumor



Gross tumor of a mouse injected with saline followed by Evans blue dye.

LPS PMNP Tumor

Gross tumor of a mouse injected with LPS PMNPs followed by Evans blue dye.

References

Cupaioli FA, et al. Engineered nanoparticles. How brain friendly is this new guest? Prog Neurobiol. 2014 Aug-Sep;119-120:20-38. Frosina G. Nanoparticle-mediated drug delivery to high-grade gliomas. Nanomedicine. 2016 May;12(4):1083-93.Karim R, et al. Nanocarriers for the treatment of glioblastoma multiforme. J Control Release. 2016 Apr10;227:23-37.Oberoi RK, et al. Strategies to improve delivery of anticancer drugs across the blood-brain barrier to treat GBM. Neuro Onc 2016 Jan;18(1):27-36. Patel TR. Nanocarrier-based therapies for CNS tumors. CNS Onc 2014