



An Antiangiogenic Peptide Fragment of beta-Amyloid Suppresses Glioma Proliferation, Angiogenesis, Invasiveness in a Syngeneic, Orthotopic Mouse Model.

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INTRODUCTION

The recent clinical success of bevacizumab to suppress angiogenesis, prolong of progression-free survival, and decrease tumor volume is proof of principle that inhibitors of angiogenesis are an effective approach for the treatment of human glioblastoma. Glioma invasion, however, remains a serious, unanswered clinical problem. An important source of drug discovery in glioblastoma anti-angiogenesis and anti-invasion research are naturally occurring inhibitors that play a role in health and disease within the central nervous system.

We previously reported that the full length A β 1-40 amyloid protein is a dose-dependent inhibitor of angiogenesis that also suppresses human U87 glioblastoma subcutaneous xenografts in nude mice (Paris D et al., *Angiogenesis*, 2004). We subsequently characterized a small peptide sequence of the Abeta amyloid, VHHQKLVFF, as a potent and novel anti-angiogenic molecule (Patel NS et al, *Amyloid*, 2008).

In order to translate these findings to the clinic, we evaluated the effect of this peptide on a syngeneic, orthotopic model characterized by rapid, invasive growth.

AIM

The aim of this study was to determine effectiveness of A β in the treatment of malignant glioma.

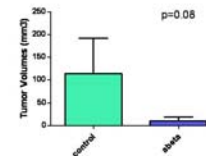
METHODS

C57BL/6 immunocompetent mice were implanted with 1 x 10⁵ cells in 2 μ l GL261 syngeneic murine primary glioma. The animals were randomized to two groups, received intraperitoneal injection of either the active A β 11-20 50 mg/kg/day (n=10) or control (n=12) comprised of inactive vehicle. The treatment started on day 9 after tumor implantation and continued until day 27 when the brains were harvested and stained with H&E (invasion), Ki-67 (proliferation) and CD31 (microvascular density).

RESULTS

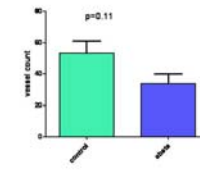
- The gliomas in the treated animals were much smaller with a decreased microvascular density (angiogenesis).
- There was an inhibition of glioma invasiveness in the treated mice.
- The proliferation rate was reduced in the gliomas in the treated group, $P \leq 0.02$.
- Toxicity related to the drug was not observed.

Tumor Volumes



Tumors from animals treated with A β were significantly smaller than control.
Animals tolerated the treatment well with no weight loss.

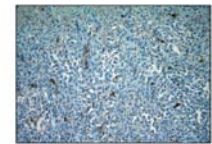
CD31:



There was a reduction in number of microvessels in the tumors of animals treated with abeta

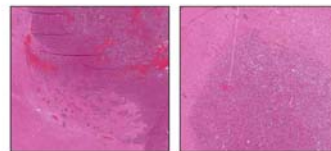


Control



A β

H&E staining:

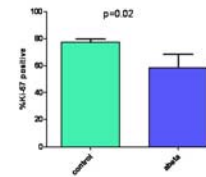


Control

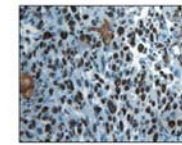
A β

Invasion is reduced in tumors from animals treated with A β compared with control.

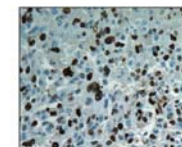
Ki-67:



There was a statistically significant reduction in proliferating cells in tumors from animals treated with A β compared to control.



Control



A β

CONCLUSIONS

These results indicate that systemic delivery of a potent, antiangiogenic motif of the A β amyloid protein leads to a reduction in glioma proliferation, angiogenesis, and invasiveness. Furthermore, parallel experiments in a genetically-engineered model with animals that overexpress the amyloid precursor protein (APP) also showed reduction of glioma growth and angiogenesis (Paris D, Mullan M, Banasiak M, Yee G-T, Murphy, S., Brem S, unpublished data). Taken together, these findings warrant further studies to determine the pharmacokinetics and toxicology in preclinical models to warrant consideration for phase I clinical trials for patients with glioblastoma.

ACKNOWLEDGEMENTS

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