NOVEL APPROACHES FOR NEUROINFLAMMATION AND BARRIER PERMEABILITY IN BRAIN METASTASIZING MELANOMA

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Supplemental Video

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Background: Melanoma is a tumor produced by the malignant transformation of melanocytes. Although this usually occurs on the skin, it can arise in other locations where neural crest cells migrate such as the GI tract and brain. Melanoma is commonly found in patients younger than 55 years and accounts for the third-highest number of lives lost across all cancers. Brain metastasis occurs in almost 50% of melanoma patients and is linked to astrogliosis, a process reactive to neuronal damage which increases neuroinflammation and increases permeability of the Blood Brain Barrier (BBB). Current BRAF/MEK inhibition therapies which target pathways involved in uncontrolled cell proliferation and resistance to apoptosis show limited success in improving survival. Thus, a critical need exists to develop more effective therapies aimed at improving this neuroinflammation and decreasing BBB permeability. ATN-161 is a vascular α5β1 integrin inhibitor that has been clinically validated in treating glioblastoma via anti-angiogenetic mechanisms that deprive tumors of oxygen delivery and restore tight junction control at the blood brain barrier (BBB).

Goals: In this review, we summarize the mechanisms of melanoma metastasis to the brain and hypothesize how ATN-161 may be used as treatment.

Methods: Pubmed, Web of Science, and Embase databases were searched using relevant key terms and articles were included if mechanisms of metastasis or prevention of melanoma transmigration across the BBB were discussed.

Results: We found that melanoma increases production of metalloproteinases to alter the extracellular matrix (ECM) thereby increasing levels of neuroinflammation and BBB permeability. ATN-161 may work to reduce metalloproteinase production and strengthen BBB tight junctions through claudin-5 interactions, thus preventing the deleterious effects of metastasis. Additionally, animal studies have shown that ATN-161 increases doxorubicin delivery to melanoma cells to increase survival time, further supporting its potential therapeutic use.

Conclusion: Our review summarizes the evidence for ATN-161 as a potential therapeutic for metastasizing melanoma by reducing neuroinflammation and BBB permeability and acting as an improved delivery agent for existing BRAF inhibitors.

Learning Objectives

1) Describe mechanisms of melanoma metastasis to the brain.

2) Identify ways that ATN-161 may be able to target melanoma mechanisms of metastasis to the brain as a potential novel therapeutic.