



Attenuated Invasiveness of CNS Metastases in Their New “Soil”

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Introduction

Brain metastases occur in up to 40% of cancer patients. Paget’s “seed and soil” hypothesis states that the survival and proliferation of these cancer cells is dependent on favorable interactions with its new microenvironment. However, it does not address the attenuated invasiveness of these metastatic tumors in the brain given the highly malignant potential of these cancer cells. Despite the breakdown of the blood-brain barrier, there is a sharp demarcation between tumor and brain both on radiographic imaging and histology. This study was designed to evaluate and confirm the interaction between metastatic tumor cells and their new “soil”.

Methods

Renal and cervical cancer cell lines were seeded with human astrocytes into 2-well co-cultivation systems with a 500-micron gap for 2D invasion assay. The dividing insert was then removed and cellular migration was recorded with video microscopy. Double immunofluorescence staining was also performed to examine the tumor-glial interface on paraffin-embedded sections of cervical cancer, colorectal cancer, and melanoma.

Results

Video microscopy demonstrated development of a clear interface between the metastatic tumor cells and astrocytes. Astrocytes exhibited cellular activation, gliotic changes and established boundaries at the interface. Immunofluorescence stains showed sharp demarcations between tumor cells and astrocytes for both cervical and colorectal cancer. This interface was not as clearly delineated between melanoma and astrocytes.

Conclusions

Malignant tumors that are known to be aggressive in their primary organ appear to be less invasive once they metastasize to the CNS. There is a clear demarcation of tumor-brain interface as demonstrated with our study in contrast to the infiltrative pattern seen with malignant primary brain tumors in their native soil. This attenuated invasiveness may be dictated more by the microenvironment sustained by the glial cells rather than the pathology of the primary tumor. Comparison between the native and new microenvironments prompts further investigation.

Learning Objectives

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

- 1)Describe the “seed and soil” hypothesis of metastases
- 2)Discuss the sharp interface between metastases and astrocytes
- 3)Identify the importance of expanding upon the “soil” hypothesis to understand the impact of the microenvironment in limiting the invasiveness of metastatic tumors in the CNS and potential for developing future therapeutic options.

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