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EDA Fibronectin: A Regionally Specific Driver of Glioblastoma Pathogenesis

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Introduction

Glioblastoma is an aggressive cancer with a dismal median survival of under two years from diagnosis. A defining feature of these tumors is their invasiveness, which enables escape from resection and drives recurrence. The attributes that make this cancer so invasive are poorly understood, but the extracellular matrix is suspected to play a considerable role. One candidate is Extra Domain A expressing fibronectin (EDA-FN), a splice variant that has been associated with other malignancies.

Methods

We collected site-directed biopsies from glioblastoma patients. Ex vivo analysis was performed using immunohistochemistry (IHC), quantitative reverse-transcription PCR (RT-qPCR), fluorescence-activated cell sorting (FACS) and western blotting.

Results

Analysis of site-directed biopsies determined that EDA-FN was expressed at significantly higher rates in the subventricular zone (SVZ), a tumor location known to have a worse prognosis due to the presence of native stem cells. The expression level of EDA-FN was directly and significantly associated with upregulated mesenchymal genetic markers ($p<0.001$), which have also been associated with worse patient outcomes. Tumor FACS revealed that the source of EDA-FN was cancer associated fibroblasts (CAFs) which comprised 9% of GBM cells in the SVZ vs. 2% of GBM cells outside the SVZ and were not present in SVZ specimens from epilepsy cases ($P<0.001$). CAFs were recruited by factors secreted by the GBM stem cells found in the SVZ. IHC revealed that EDA- FN forms a scaffolding network and is spatially associated with CAFs. Lastly, culturing macrophages with EDA-FN demonstrated more M2 pro-tumoral polarization than was seen in control FN without EDA.

Conclusions

We defined a cascade by which stem cells in the SVZ recruit CAFs, which in turn produce EDA-FN in the SVZ. EDA-FN induces M2 polarization and is associated with mesenchymal gene expression. Given the specificity of CAFs and EDA-FN to cancer, both may represent viable therapeutic targets.

Learning Objectives

1) Understand the role that fibronectin likely plays in GBM pathogenesis,
2) appreciate how ECM may act as a driver for cancer progression