Tenascin-C Regulates Glioblastoma Stem-like Cell Go-or-grow by Modulating Tumor Microenvironment

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Introduction

Glioblastoma multiforme (GBM) is the most frequent and aggressive primary brain tumor in adults. Recent research on cancer stroma indicates that the brain microenvironment plays a substantial role in brain tumor malignancy and treatment responses to current anti-tumor therapy. In this work, we investigated the effect of alterations in brain tumor extracellular matrix tenascin (TNC) on brain tumor growth patterns including proliferation and invasion. TNC is a multimodular glycoprotein found in malignant brain tumors and mediates cell-cell and cell-matrix interactions.

Methods

We studied TNC gain-of-function and loss-of function in GBM stem-like neurospheres (GSCs), whose in vivo growth pattern closely replicates human GBM.

Learning Objectives

By the conclusion of this session, participants should be able to describe the influence of TNC in the tumor microenvironment on

Results

TNC knockdown with shRNAs promoted GSC adhesion and actin cytoskeleton organization. Inhibition of focal adhesion kinase (FAK) pathway activation significantly inhibited (>75%) TNC knockdown-mediated cell adhesion. Yet, TNC loss-of-function or exogenous TNC had no effect on cell growth in vitro. The effect of TNC loss-of-function on in vivo tumor growth was assessed using GSC intracranial xenografts. When TNC expression was decreased in the tumor microenvironment, we detected decreased tumor cell invasion accompanied by increased tumor size, suggesting that TNC regulates the “go-or-grow” phenotypic switch of GSC in vivo. We further demonstrate that decreased TNC in the tumor microenvironment significantly altered the interactions between tumor cells and surrounding non-tumor endothelial and microglial cells, influencing the tumor growth pattern.

Conclusions

Our findings suggest that increased understanding of how TNC in the tumor microenvironment influences interactions between tumor cells and surrounding non-tumor cells will benefit novel combinatory anti-tumor strategies to treat malignant brain tumors.

References

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