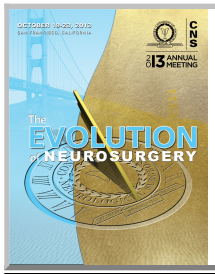

GDNF Mediates Glioblastoma-induced Microglia Attraction but Not Astrogliosis

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Introduction

High-grade gliomas are the most common primary brain tumors. Their malignancy is promoted by the complex crosstalk between different cell types in the central nervous system. Microglia/brain macrophages infiltrate high-grade gliomas and contribute to their progression.

Methods

To identify factors that mediate the attraction of microglia/ macrophages to malignant brain tumors, we established a glioma cell encapsulation model that was applied in vivo. Mouse GL261 glioma cell line and human high-grade glioma cells were seeded into hollow fibers (HF) that allow the passage of soluble molecules but not cells. The glioma cell containing HF were implanted into one brain hemisphere and simultaneously HF with non-transformed fibroblasts (controls) were introduced into the contralateral hemisphere.

Results

Implanted mouse and human glioma- but not fibroblast-containing HF attracted microglia and up-regulated immunoreactivity for GFAP, which is a marker of astrogliosis. In this study, we identified GDNF as an important factor for microglial attraction: (1) GL261 and human glioma cells secret GDNF, (2) reduced GDNF production by siRNA in GL261 in mouse glioma cells diminished attraction of microglia, (3) over-expression of GDNF in fibroblasts promoted microglia attraction in our HF assay. In vitro migration assays also showed that GDNF is a strong chemoattractant for microglia. While GDNF release from human or mouse glioma had a profound effect on microglial attraction, the glioma-induced astrogliosis was not affected. Finally, we could show that injection of GL261 mouse glioma cells with GDNF knockdown by shRNA into mouse brains resulted in reduced tumor expansion and improved survival as compared to injection of control cells.

Conclusions

We identified GDNF as a HG-glioma released factor that specifically leads to microglial attraction. Thus, our study supports the idea that microglia play an important role in tumor growth, invasion and progression and thus can become a novel target for therapeutic strategies.

Learning Objectives

High-grade gliomas (HG-gliomas) are most aggressive primary tumors of the central nervous system (CNS). Recent data indicate that blockade of microglia infiltration into HG-gliomas could be a novel therapeutic target in neuro-oncology. We could identify GDNF as a soluble factor that regulate the cross talk between glioma cells and glial cells.

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