“Role of CXCR4 and CXCR7 in Glioma Invasion”

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Gliomas are the most common type of primary brain tumor in adults. Histologically, gliomas consist of a tumor mass with an ill-defined border. Instead of metastasizing to distal organs, gliomas characteristically spread through the brain parenchyma as individual cells. As a result of glioma invasion, after surgical resection of the tumor mass, a recurrent tumor typically occurs within a 2 cm margin of the primary tumor. Largely due to decreased proliferation rate and increased resistance to apoptosis, invading glioma cells are extremely resistant to radiation therapy and chemotherapy and render successful treatment nearly impossible. Invasion is therefore a hallmark of malignant gliomas and is the main reason for therapeutic failure and recurrence of the tumor. Thus, there is a dire need to understand the molecular mechanisms governing glioma invasion in order to develop effective anti-invasive therapies.

Our studies investigated the role of two G-protein coupled receptors, CXCR4 and CXCR7, in glioma invasion. We observed that hepatocyte growth factor (HGF), a cytokine implicated in glioma cell migration, upregulated CXCR4 expression and increased glioma cell migration towards stromal cell-derived factor (SDF)-1α, the ligand of CXCR4. HGF-mediated CXCR4 induction and migration towards SDF-1α was mediated by NF-κB. Our findings demonstrate that a crosstalk mediated by NF-κB exists between the SDF-1α/CXCR4 and HGF/c-Met axes relevant to glioma cell migration.

CXCR7 has recently been identified as the second SDF-1α receptor. Our data also demonstrate that hypoxia upregulates CXCR7 expression and CXCR7 mediates the migration of glioma cells towards SDF-1α. Inhibition of CXCR4 or knockdown of CXCR7 decreased levels of SDF-1α-induced phosphorylation of ERK1/2 and Akt. Immunoprecipitation of CXCR4-HA from glioma cells led to the detection of co-precipitated CXCR7. Our findings indicate the presence of a functional heterodimer of CXCR4/CXCR7 that mediates glioma cell migration towards SDF-1α.

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