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Composite Hydrogel Matrices of Chondroitin 4- and 4,6-Sulfated Glycosaminoglycans Significantly Enhance Glioma Cell Invasion

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Glioblastoma multiforme (GBM) is an aggressive, devastating type of brain tumor characterized by a highly invasive nature. Chondroitin sulfate proteoglycans (CSPGs) and their glycosaminoglycan (GAG) side chains are important elements in the brain extracellular matrix (ECM) and have been implicated in promoting tumor invasion. However, conclusive evidence to suggest CSPGs or the associated CS-GAGs induce brain tumor invasion is currently lacking. We aim to provide evidence suggesting that tumor cell invasion can be influenced by the level of sulfation of CS-GAGs in the tumor ECM. This was tested in vitro by encapsulating the glioblastoma cell line U87MG-EGFP into CS-A (4-sulfated), composite CS-A/E (4,6-sulfated), hyaluronic acid, and agarose hydrogels. We hypothesize that the sulfation of CS-GAGs influences tumor cell migration through a CXCL12/CXCR4 chemokine-mediated mechanism. Choice assays using microfluidics devices showed preferential cell migration into composite CS-A/E hydrogels ($p<0.05$). Immunohistochemistry for the cytoskeletal components FAK and vinculin demonstrated that cells encapsulated in CS-GAG gels express significantly more colocalization than control treatments ($p<0.05$). Chemotaxis assays with the chemokine CXCL12 suggest that, after three hours, GBM cells migrate further into composite gels containing CXCL12 than those without, displaying potential for chemokine-GAG affinity ($p<0.05$). In sandwich ELISA assays, oversulfated CS-GAGs showed affinity for binding CXCL12 compared to other gel groups ($p<0.5$). QRT-PCR assays further demonstrate the significant upregulation of the CXCL12 chemokine receptor CXCR4 and the CSPG receptor LAR in U87MG-EGFP cells encapsulated in CS-GAG gels. These results suggest that glioma malignancy may be directly influenced by the level of sulfation of CS-GAGs.