Adult mouse subventricular zones stimulate glioblastoma stem cells specific invasion through CXCL12/CXCR4 signaling.

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Abstract

BACKGROUND: Patients with glioblastoma multiforme (GBM) have an overall median survival of 15 months. This catastrophic survival rate is the consequence of systematic relapses that could arise from remaining glioblastoma stem cells (GSCs) left behind after surgery. We previously demonstrated that GSCs are able to escape the tumor mass and specifically colonize the adult subventricular zones (SVZs) after transplantation. This specific localization, away from the initial injection site, therefore represents a high-quality model of a clinical obstacle to therapy and relapses because GSCs notably retain the ability to form secondary tumors.

METHOD: In this work, we questioned the role of the CXCL12/CXCR4 signaling in the GSC-specific invasion of the SVZs.

RESULTS: We demonstrated that both receptor and ligand are respectively expressed by different GBM cell populations and by the SVZ itself. In vitro migration bio-assays highlighted that human U87MG GSCs isolated from the SVZs (U87MG-SVZ) display stronger migratory abilities in response to recombinant CXCL12 and/or SVZ-conditioned medium (SVZ-CM) compared with cancer cells isolated from the tumor mass (U87MG-TM). Moreover, in vitro inhibition of the CXCR4 signaling significantly decreased the U87MG-SVZ cell migration in response to the SVZ-CM. Very interestingly, treating U87MG-xenografted mice with daily doses of AMD3100, a specific CXCR4 antagonist, prevented the specific invasion of the SVZ. Another in vivo experiment, using CXCR4-invalidated GBM cells, displayed similar results.

CONCLUSION: Taken together, these data demonstrate the significant role of the CXCL12/CXCR4 signaling in this original model of brain cancer invasion.

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KEYWORDS: CXCL12; cancer stem cells; invasion; stem cell microenvironment

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