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CXCL12-CXCR4 axis potentiates stemness of glioma cells

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Abstract

Glioblastoma multiforme (GBM) is a common primary tumor of the central nervous system. The change of cell stemness is one of the important characteristics of tumors including GBM, which is a cause and effect of tumor recurrence and metastasis. Previously, a large number of studies have shown that chemokines and their receptors can promote the stemness of tumor cells. Upon binging to the receptor special CXCR4, CXCL12 is involved in the proliferation, invasion and metastasis of tumor cells. Here we report the impact of CXCL12-CXCR4 axis on cancer stem cells (CSCs) in GBM.

GBM is the most well-known and most harmful essential glial tumor in grown-ups, portrayed by a perpetually poor result and constrained helpful choices (Dolecek et al., 2012). Standard GBM the executives includes maximal careful resection, trailed by radiotherapy with attending and adjuvant chemotherapy with temozolomide, however by and large GBM quickly backslides. Accessible medicines at backslide are to a great extent ineffectual and middle by and large endurance of GBM patients is around 15 months.

There is expanding proof that tumor improvement, development, repeat and protection from chemo-and radio-treatment is identified with the nearness of a cell subpopulation, named malignancy undifferentiated organisms (CSCs), these days distinguished in various human hemopoietic and strong diseases, including GBM. Proficient CSC destruction speaks to the ineludible objective to forestall tumor backslide and along these lines an objective for all new anticancer methodologies.

Close to its useful articulation in early stage pluripotent foundational microorganisms, in grown-ups CXCL12/CXCR4/R7 hub controls tissue-explicit undifferentiated organism expansion (Singh et al., 2013). Comparable capacities have been theorized to happen additionally in CSCs. Along these lines the meaning of systems and downstream arbiters of CXCR4/R7 enactment by CXCL12, in typical and harmful separated cells, their begetters, and in ordinary and CSCs, is profoundly pertinent for both malignant growth science and point of view restorative focusing on.

CKs are vital controllers of cell movement, bond, and multiplication during aggravation and invulnerable reconnaissance as well as during CNS advancement. Specifically, alongside provocative or homeostatic leukocyte relocation, CXCL12 holds an early stage job, exceptionally moderated through the development, in the guideline of undeveloped and grown-up foundational microorganism directional movement. The principal proof of the capacity of CXCL12 in neural advancement was recommended by the deadly phenotype of CXCR4-and CXCL12-knockout mice (Ma et al., 1998; Zou et al., 1998), both displaying strange neuronal relocation in the cerebellum, dentate gyrus and dorsal root ganglia, notwithstanding blemished lympho-myelopoiesis, and flawed vasculature and heart improvement.

During cerebellar advancement CXCR4-positive granule cell antecedents are held in the outside granule layer through their connection with CXCL12 communicated in the overlying pial meninges, guaranteeing adequate cell expansion and permitting the movement to the inside granule layer just when the cerebellar cortex is prepared to get them. Changed CXCL12/CXCR4 collaboration causes an untimely relocation of granule antecedents and complicated layer development (Stumm et al., 2003; Huang et al., 2014). CXCL12 stays cerebellar granule antecedents and favors their multiplication synergistically with Sonic hedgehog (Shh). The CXCL12/CXCR4 hub likewise controls the digressive movement of post-mitotic neurons (Tiveron et al., 2006).

Methods:

Bioinformatics software was used, based on TCGA, to analyze of the potential correlation between CXCL12-CXCR4 axis and stem-related genes (OCT4, SOX2, NANOG). Quantitative real time polymerase chain reaction (qRT-PCR), western blotting and sphere forming ability analyses were performed to access the effect of CXCL12-CXCR4 axis on GBM cell stemness in vitro. Different numbers of cells were planted under the skin of nude

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mice to observe the tumor formation rate and tumor growth rate, so as to detecting the stemness of glioma cells in vivo.

Results:

Compared with normal brain tissue, the expression of CXCL12-CXCR4 axis in glioma tissue was significantly increased ($p<0.05$) and was negatively correlated with the pathological grade of GBM patients. CXCR4 mRNA was positively correlated with stemness-related gene (OCT4, SOX2, NANOG) mRNA expression levels in GBM. qRT-PCR, western blotting and sphere forming ability analyses illustrated that CXCL12-CXCR4 axis maintained stemness self-renewal and promoted proliferation and metastasis of glioma cell in a time- and concentration-dependent manner in vitro. Compared with the PBS group, the expression of stemness-related proteins of glioma cells in the CXCL12 co-incubation group was significantly increased and the ability of forming spheres was significantly enhanced ($p<0.05$). After treatment of plerixafor, a selective CXCR4 antagonist, glioma cell stemness-related proteins and the ability of forming spheres were effectively inhibited ($p<0.05$). Next, we constructed the interference plasmid of CXCR4. The results of western blotting and sphere forming ability analyses found that the level of stemness-related proteins in the interference CXCR4 group was significantly reduced compared with the control group, and the ability of forming spheres was significantly reduced ($p<0.05$). However, compared with the control group, overexpression of CXCR4 significantly increased the expression level of stemness-related proteins and the ability of forming spheres in glioma cells ($p<0.05$). The results of nuclear plasma isolation experiments showed that glioma cells co-incubated with CXCL12 could promote β-catein nuclear ectopia, which may be the potential mechanism of CXCL12-CXCR4 axis promoting tumor stemness ($p<0.05$). Finally, we carried out experimental verification on mice. U87MG cancer cells were cocultured with PBS, CXCL12(80 ng/mL), or CXCR4 knockdown cancer cells (sh-CXCR4), and then injected subcutaneously into nude mice for the indicated cell number (1×104, 1×105 and 1×106 cells/mouse were injected, respectively).

U87MG cells cocultured with CXCL12 showed significantly higher tumor initiating capacity than the other groups. The tumor volume of sh-CXCR4 group was significantly smaller than that of PBS group. 4/4 mice developed tumors in each group until the cell number reached 1×106, but tumors derived from CXCL12 coculture group were larger than the other groups ($p<0.05$).

Conclusion:

CXCL12-CXCR4 axis promotes the malignant transformation of tumors by promoting cell stemness, which provides new targets and evidence for targeted therapy of GBM.

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