Glioma stem cell

Glioma initiating cells (GICs), also known as glioma stem cells, display the capacity to recapitulate the functional diversity within the tumor.

Glioma stem cells are maintained in specialized microenvironments, but whether, or how, they undergo lineage progression outside of these niches remains unclear. Brooks et al. identified the white matter as a differentiative niche for glioblastomas with oligodendrocyte lineage competency. Tumor cells in contact with white matter acquire pre-oligodendrocyte fate, resulting in decreased proliferation and invasion. Differentiation is a response to white matter injury, which is caused by tumor infiltration itself in a tumor-suppressive feedback loop. Mechanistically, tumor cell differentiation is driven by selective white matter upregulation of SOX10, a master regulator of normal oligodendrogenesis. SOX10 overexpression or treatment with myelination-promoting agents that upregulate endogenous SOX10, mimic this response, leading to niche-independent pre-oligodendrocyte differentiation and tumor suppression in vivo. Thus, glioblastoma recapitulates an injury response, and exploiting this latent program may offer treatment opportunities for a subset of patients [1)].

Glioblastoma is largely due to glioma stem cells (GSCs) that escape from total resection of gadolinium (Gd)-enhanced tumor on MRI.

They contribute to the tumor’s heterogeneous nature, therapeutic resistance, and, thereby, inevitable tumor recurrence [2) 3)].

Inoue et al. investigated the relationship of tumor volume between MRI and 11C methionine positron emission tomography and also the relationship between Met uptake index and tumor activity. In ten patients, tumor-to-contralateral normal brain tissue ratio (TNR) was calculated to evaluate metabolic activity of Met uptake areas which were divided into five subareas by the degrees of TNR. In each Glioblastoma, tumor tissue was obtained from subareas showing the positive Met uptake. Immunohistochemistry was performed to examine the tumor proliferative activity and the existence of glioma stem cells (GSCs). In all patients, the volume of Met uptake area at TNR $\leqq$ 1.4 was larger than that of the Gd-enhanced area. The Met uptake area at TNR 1.4 beyond the Gd-enhanced tumor was much wider in high invasiveness-type Glioblastomas than in those of low invasiveness type, and survival was much shorter in the former than the latter types. Immunohistochemistry revealed the existence of GSCs in the area showing Met uptake at TNR 1.4 and no Gd enhancement. Areas at TNR $>$ 1.4 included active tumor cells with a relatively high Ki-67 labeling index. In addition, it was demonstrated that GSCs could exist beyond the border of the Gd-enhanced tumor. Therefore, to obtain maximum Glioblastoma extent of resection, including infiltrating GSCs, an aggressive surgical excision that includes the Met-positive area at TNR 1.4 should be considered [4)].

Accumulated evidence suggests that elevated resistance of Glioblastoma to both chemotherapy and radiotherapy is, at least in part, due to the presence of a small population of glioma stem cells (GSC). [5)].

These cells are associated with vascular niches which regulate GSC self-renewal and survival.

Studies suggest that while blood vessels support glioma stem cells, these tumor cells in turn may regulate and contribute to the tumor vasculature by transdifferentiating into endothelial cells directly or through the secretion of regulatory growth factors such as vascular endothelial growth factor (VEGF) and hepatoma derived growth factor (HDGF) [6].

Glioma stem cells expressed higher mRNA levels of protoporphyrin IX (PpIX) biosynthesis enzymes and its transporters PEPT1/2 and ABCB6, when compared to the parental A172 glioma cells. Consistently, flow cytometry analysis revealed that upon incubation with ALA, GSLCs accumulate a higher level of PpIX. Finally, Fujishiro et al., showed that GSLCs were more sensitive to 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) than the original A172 cells, and confirmed that all patient-derived glioma sphere lines also showed significantly increased sensitivity to ALA-PDT if cultivated under the pro-stem cell condition. This data indicate that ALA-PDT has potential as a novel clinically useful treatment that might eliminate Glioblastoma stem cells that are highly resistant to the current chemo- and radio-therapy [7].

They express CD133 gene and other genes characteristic of neural stem cells and posses the self-renewal potential. Cancer stem cells derived from glioblastoma are capable recapitulate original polyclonal tumors when xenografted to nude mice.

Glioma stem cells (GSCs) in individual High-grade glioma (HGG) subtypes remain poorly characterized. Recently genome-wide transcriptional analysis identified two mutually exclusive GSC subtypes with distinct dysregulated signaling and metabolic pathways. Analysis of genetic profiles and phenotypic assays distinguished proneural (PN) from mesenchymal (MES) GSCs and revealed a striking correlation with the corresponding PN or MES HGGs. Similar to HGGs with a MES signature, MES GSCs display more aggressive phenotypes both in vitro and in vivo. Furthermore, MES GSCs are markedly resistant to radiation as compared with PN GSCs, consistent with the relative radiation resistance of MES Glioblastoma compared with other subtypes. A systems biology approach has identified a set of transcription factors as the master regulators for the MES signature. Metabolic reprogramming in MES GSCs has also been noticed with the prominent activation of the glycolytic pathway, comprising aldehyde dehydrogenase (ALDH) family genes [8].

Molecular regulators

Despite the great progress achieved over the last decades, defining the key molecular regulators of GICs has represented a major obstacle in this field.

Nishikawa et al. investigated the existence and functions of GSCs in the tumor periphery, which is considered to constitute the invasion niche for GSCs in Glioblastoma, by analyzing expression of stem cell markers and stem cell-related molecules and measuring particular activities of cultured GSCs. In addition, the relationship between GSCs expressing particular stem cell markers and pathological features on MRI and prognosis in Glioblastoma patients was analyzed. We showed that GSCs that express high levels of CD44 are present in the tumor periphery. We also found that vascular endothelial growth factor (VEGF) is characteristically expressed at a high level in the tumor periphery.

Cultured GSCs obtained from the tumor periphery were highly invasive and have enhanced migration phenotype, both of which were markedly inhibited by CD44 knockdown. Higher expression of CD44 in the tumor periphery than in the core was correlated with a highly invasive feature on MRI and was associated with early tumor progression and worse survival, whereas lower expression of CD44 in the tumor periphery corresponded to low invasion and was associated with longer survival. The low invasion type on MRI tended to show high levels of VEGF expression in the tumor periphery, thus presenting the tumor with high proliferative activity. These results imply the significance of GSCs with high levels of CD44 expression in the tumor periphery compared to the core, not only in tumor invasion but also rapid tumor progression and short survival in patients with Glioblastoma [9].

Differentiated glioblastoma cell (DGC)s preferentially expressed brain derived neurotrophic factor (BDNF), whereas glioblastoma stem cells (GSCs) expressed the BDNF receptor NTRK2. Forced BDNF expression in DGCs augmented GSC tumor growth. To determine molecular mediators of BDNF-NTRK2 paracrine signaling, we leveraged transcriptional and epigenetic profiles of matched GSCs and DGCs, revealing preferential VGF expression by GSCs, which patient-derived tumor models confirmed. VGF serves a dual role in the glioblastoma hierarchy by promoting GSC survival and stemness in vitro and in vivo while also supporting DGC survival and inducing DGC secretion of BDNF. Collectively, these data demonstrate that differentiated glioblastoma cells cooperate with stem-like tumor cells through BDNF-NTRK2-VGF paracrine signaling to promote tumor growth [10].

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