Editorial

Stem Cell INVESTIGATION

Cross-talk between tumor stem cells and tumor cells: a glioblastoma strategy to promote malignancy

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Glioblastoma multiforme (GBM) is the most frequent and malignant type of primary tumors of the central nervous system. Despite current advances in multimodal therapies, involving advanced surgery, radio- and chemotherapy, and the development of innovative targeted therapies the outcome for patients with GBM is nearly always fatal, with a median survival time of only 12–15 months (1). Various obstacles hamper development of effective therapies, including cellular and molecular heterogeneity, high proliferation rate, pervasive tumor cell infiltration, intensive angiogenesis, therapeutic resistance, and, not last, the lack of a full understanding of the pathobiology of the disease.

Increasing evidence supports that the GBM microenvironment has a tremendous influence over the tumor growth and spread (2). Indeed, GBM tumor cells can be exposed to diverse cellular niches (e.g., perivascular, hypoxic, perinecrotic), influenced by different cell populations and enriched with specific repertoires of signal molecules (growth factors, cytokines, chemokines, etc.). These environmental cues steer tumor cell fate, affecting quiescence, proliferation, survival and invasion (3). Several studies indicate that GBM cells and GBM-like stem cells (GSCs) are able to recruit different normal brain cells, such as microglia, astrocytes, endothelial and immune cells, and induce them to modify the tumor microenvironment with pro-tumoral signals (4,5).

Despite intensive studies over the past decade on the influence of GSC interactions with different normal brain cells have been observed in many settings and are known to contribute to crucial tumor properties in GBMs, it is unclear whether GBM cells contribute to GSC properties and/or vice versa. In a study in *Cell Stem Cells*, Wang *et al.* (6) reported that, by secreting distinct molecules, GSCs and differentiated GBM cells (DGC) form a molecular dialogue that serves a dual role in the GBM by promoting not only GSC stemness and survival, but also supporting DGC survival and secretion. In immunocompromised mice, after intracranial co-transplantation with patient-derived GSCs with DGCs, the Authors first observed accelerated tumor growth and reduced survival compared to xenograft-bearing mice transplanted with GSCs alone or GSCs with fibroblasts, suggesting a contribution from the DGCs in GSCs tumorigenicity. Following experiments demonstrated that the brain-derived neurotrophic factor (BDNF), previously demonstrated to act as proliferative signal in GBM (7), was highly secreted by, and mRNA levels were up-regulated in DGCs compared to matched GSCs. The Authors then hypothesized that GSCs would express NTRK2 to mediate the paracrine effects of BDNF. In agreement, they found that the BDNF receptor NTRK2 was upregulated in GSCs and was specifically expressed by tumor cells that were positive for the GSC marker SOX2. The Authors went on to evaluate the *in vivo* effect of BDNF and showed that orthotopic co-transplantation of GSCs and BDNF-depleted DGCs resulted in reduced tumor growth compared with both that of GSCs and BDNF-expressing DGCs. Moreover, BDNF transduction of GSCs revealed enhanced intracranial tumor growth and reduced survival outcome when compared to original GSCs.

Further experiments revealed intriguing characteristics

of the DGC-GSCs interaction. First, BDNF induced the upregulation of the neurotrophic peptide VGF specifically in GSCs through activation of the PI3K-AKT signaling, and VGF was shown to be critical for GSC growth and stemness. Second, VGF promoted increased DGC viability and growth. Third, VGF-depleted GSCs intracranially transplanted into mice exhibited increased survival and the absence of tumors.

These findings demonstrate that DGCs and GSCs impact each other in a reciprocal fashion via their production of BDNF and VGF, respectively. Indeed, this cross-talk promotes synergy amongst these cells and thereby amplifies the tumorigenic potential of the individual cell populations. As a result, this interconnection benefits the tumor, but also implies that therapies that down-regulate one population may also reduce the other cell populations.

There are many strengths in the paper. However, it should be noted that the novel findings were based on data obtained in $CD133^+$ GSCs. Although CD133 is classically associated with GSCs, it is also expressed in normal neural stem cells. Moreover, it has been shown that $CD133^-$ GSCs exhibit different growth properties and molecular profiles (8), and, when implanted in rat brains, are capable of inducing tumors and give rise to $CD133^+$ cells (9). Thus, further research is needed to clarify the role of $CD133^-$ GSCs before future studies aimed at developing therapies that interfere with GSCs-DGCs interactions such that the potent synergistic activity of these cells is neutralized.

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Footnote

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