

# WhatsApp com between glioma stem cells and differentiated cells to sustain tumor growth

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Glioblastoma is the most common malignant brain tumor with extremely poor patient survival of approximately 15 months (1). This poor prognosis reflects therapeutic resistance and is attributed, at least in part, to the existence of a subset of cells named glioma stem-like cells (GSCs) (2,3). Numerous studies indicate that glioblastoma is heterogeneous, composing of a rare population of GSCs and more differentiated glioma cells (DGCs). Although individual tumors may contain several types of GSCs in terms of molecular expression and/or gene mutations, GSCs share the common characteristic of therapy resistance. This may be due to quiescent status of GSCs (4), efficient DNA repair after therapy treatment (5), high drug efflux of ABC transporters (6) and/or Notch survival signaling (7). Cancer cell stem cells (CSCs) are increasingly reported to interact with non-CSCs to sustain tumor aggressiveness. Using an elegant set of studies, Wang *et al.* (8) show that DGCs and GSCs interact in a dynamic and bidirectional manner to support tumor growth. The authors demonstrate that DGCs secrete brain-derived neurotrophic factor (BDNF) and GSCs express the specific tyrosine kinase receptor of BDNF, NTRK2 (TrkB). Apart from its well-known neurotrophic functions, BDNF promotes cancer cell proliferation, migration, invasion of different tissues of origin (9). Neurotrophins including BDNF are also able to stimulate proliferation of GSCs through different pathways including ERK and AKT activation (10,11). The findings by Wang *et al.* place VGF (non-acronymic) as a central element linking GSC and DGCs to support tumor growth. *VGF* is a neurotrophin-induced gene, which was first identified by Levi *et al.* based on its rapid induction by nerve

growth factor (NGF) (12). *VGF* is also induced by BDNF and neurotrophin-3 (NT-3), in cortical or hippocampal neurons (13). The 68 kDa VGF polypeptide can be processed by the prohormone convertases to generate specific peptides including TLQP-62 and neuroendocrine regulatory peptides (14,15). These peptides have been associated with a number of neuroendocrine roles such as neurogenesis, energy and water homeostasis. The study of Wang and colleagues (8) illustrates a positive feedback loop in which DGCs-secreted BDNF acts in a paracrine manner to activate the tyrosine kinase receptor, NTRK2, which is expressed in GSCs. The activated NTRK2 in GSCs induces PI3K-AKT pathway activation and subsequent secretion of VGF. VGF in return stimulates GSC proliferation in an autocrine manner. Interestingly, DGCs overexpressing VGF or DGCs treated with the VGF peptide TLQP-62 exhibit also an increased proliferation, indicating that VGF is also able to promote DGC growth in a paracrine manner.

These findings illustrate the interdependence between cancer stem cells and differentiated cancer cells in glioblastoma. Interestingly, similar interactions were also reported in breast cancer in which BDNF/NTRK2 is shown to be involved in chemotherapy-induced resistance and recurrence of triple-negative breast cancers (TNBC) (16). TNBC is an aggressive subtype of breast cancer exhibiting a high recurrence rate after therapies. Yin *et al.* (16) demonstrate that paclitaxel treatment induces BDNF secretion in differentiated recurrent TNBC cells. The secreted BDNF binds to NTRK2, which is expressed in breast CSCs, leading to the expression of KLF4, a zinc finger-type transcription factor of Krüppel-like factor

family, involved in cell reprogramming and the maintenance of stemness (17,18). KLF4 is shown to be able to stimulate breast CSC renewal.

Collectively, these findings indicate that dynamic interactions of CSCs and differentiated cancer cells are essential in supporting tumor aggressiveness and resistance to therapy. Moreover, apart from differentiated cancer cells, CSCs interact also with other types of cells in their specific niches. For example, the well-described perivascular GSC niche type is composed of endothelial cells, pericytes, smooth muscle cells and fibroblasts, which interact with each other to sustain survival and renewal of GSC (19,20). Multiple interactions of GSCs with different elements in the niches are crucial for tumor development. As GSCs are resistant to conventional therapies, targeting GSCs together with supportive niches may allow more efficient therapeutic approach through the simultaneous targeting of both intrinsic and extrinsic regulators of GSCs, as well as reprogramming of DGCs into GSCs. It is therefore essential to better understand molecular mechanisms regulating CSC survival and renewal in tumor microenvironment.

The findings of Wang *et al.* (8) suggest that BDNF-NTRK2-AKT-VGF axis may be used as a potential therapeutic target to disrupt both intrinsic and extrinsic GSCs molecular regulation. Further investigation is required to determine whether this axis is activated in GSCs, and/or during reprogramming of DGCs to GSCs by conventional treatment. It will be also of importance to determine how this loop is integrated in the global GSC niche.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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