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Authors
Muthukrishnan, Sree Deepthi
Alvarado, Alvaro G
Kornblum, Harley I

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Building Bonds: Cancer Stem Cells Depend on Their Progeny to Drive Tumor Progression

Sree Deepthi Muthukrishnan[1,3], **Alvaro G. Alvarado**[1,3], **Harley I. Kornblum**[1,2,*]

[1]The Intellectual and Developmental Disabilities Research Center, The Semel Institute for Neuroscience and Human Behavior, and The Broad Stem Cell Research Center, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

[2]The Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

[3]These authors contributed equally

Abstract

Little is currently known about how cancer stem-like cells (CSCs) interact with their more restricted progeny. In this issue of *Cell Stem Cell*, Wang et al. (2018) demonstrate a novel bidirectional signaling axis between CSCs and their progeny that is mediated by brain-derived neurotrophic factor and VGF accelerating glioma progression.

Over the past decade, it has become increasingly evident that some tumors are organized in lineage hierarchies similar to their tissue of origin, and the population of cells at the apex of this hierarchy consists of cancer stem-like cells (CSCs). Multiple features of the tumorigenic process also mimic normal development and tissue regeneration processes: the plasticity and heterogeneity of CSCs and their localization into specific niches remarkably resemble that of their normal counterparts.

In glioblastoma (GBM), the most lethal form of brain cancer and other forms of glioma, there is still a significant amount of controversy regarding the existence and prevalence of glioma stem-like cells (GSCs). The most powerful evidence of a true hierarchical model comes from tumors in genetically modified mice (Chen et al., 2012). In human glioma, there are distinct subsets of cells that possess a high capacity to form tumors as xenografts and to form characteristic spheres of cells on clonal culturing that are variably termed neurospheres or gliomaspheres. These cultures appear to recapitulate the cellular heterogeneity of the original tumor, suggesting that they have the capacity to both self-renew and undergo partial differentiation or lineage specification. While it is still unclear whether GSCs exist in all human GBMs, studies from numerous laboratories support the notion that at least some GBMs are organized in a hierarchical structure with GSCs giving rise to differentiated glioma cells (DGCs). Several high-throughput sequencing studies have revealed a high degree of complexity within this hierarchy, in that single tumors may contain multiple kinds of GSCs, with different genetic and molecular expression profiles. However, all GSCs share

*Correspondence: hkornblum@mednet.ucla.edu.

common characteristics in that they are relatively resistant to most therapeutic strategies and can repopulate tumors following standard treatments, which, themselves, generally target the DGCs.

Like most stem and progenitor cells, GSCs are harbored in specific niches that provide them with signals for survival and self-renewal. Some GSCs reside in perivascular niches, which are often located toward the edge of tumors, while other GSCs may reside in the center of the tumor that is rather less vascularized, but relatively more hypoxic (Gilbertson and Rich, 2007). Diverse cell types including vascular elements, immune cells, glia, and neurons constitute these GSC niches. Using an elegant set of studies presented in this issue of *Cell Stem Cell*, Wang et al. (2018) demonstrate that DGCs play an essential role in this complex niche by providing a trophic environment for GSCs beyond simply serving as their cellular companions. They find that DGCs secrete brain-derived neurotrophic factor (BDNF) and GSCs express its cognate receptor, neurotrophic receptor kinase 2 (NTRK2), also known as TRKB. BDNF has long been regarded as a neurotrophic factor that mainly promotes survival, proliferation, and differentiation of neurons via both autocrine and paracrine signaling mechanisms. More recently, however, a role for BDNF has been established in multipotent neural stem and progenitor cells receptors (Le Belle et al., 2011), as well as in glioma (Lawn et al., 2015). In line with reports in neural progenitors (Le Belle et al., 2011), the authors show that BDNF-NTRK2 signaling activates the AKT pathway to promote growth and survival of GSCs. They also demonstrate that BDNF acts in an autocrine manner to promote the proliferation of DGCs. Importantly, they show that inhibition of BDNF production by DGCs blocks their tumor promoting effects.

A seemingly surprising finding in this study is that GSCs, themselves, regulate the production of BDNF by DGCs via VGF induction. VGF (a non-acronymic name) or “VGF nerve growth factor inducible” was discovered by Levi et al. (1985) as part of a screen for genes induced by nerve growth factor. This secreted neuropeptide has been previously implicated in the regulation of energy homeostasis, neurogenesis, synaptogenesis, and psychiatric disorders. One function attributed to VGF is in the processing of pro-BDNF into mature BDNF, and phosphorylation of its receptor TRKB in an auto-regulatory loop induced by BDNF in hippocampal neurons (Bozdagi et al., 2008). The function of VGF, however, has not been previously studied in the context of CSCs or glioma biology. In this study, the authors present novel data showing that BDNF-induced VGF secretion from GSCs promotes DGC survival and secretion of BDNF in a feedback regulatory loop. This type of regulatory feedback loop mechanism and bidirectional signaling between differentiated progeny and their parent stem or progenitor cells is a familiar theme in the context of organogenesis and tissue regeneration. Examples of such interactions have been reported between stem cells and their daughter cells through Delta-Notch signaling that maintains stemness. In more recent work, stem cells have also been shown to send feedforward signals to maintain their differentiated progeny in the airway epithelium (Pardo-Saganta et al., 2015). There are far fewer examples of studies investigating the role of differentiated progeny in regulating stemness and survival of CSCs in solid tumors. In breast cancer, it has been recently reported that mesenchymal-like progeny regulate breast stem cells through feedback signaling via WNT and FGF (Zhang et al., 2015). Findings from the current study indicate

that GSCs also depend on signals from DGCs for their survival and to propel tumor growth in GBM.

The interaction of GSCs and glioma cells, in general, and their niche is a topic of recent study. Much of this study has been focused on the role of glioma cells in maintaining a relatively suppressed immunologic state. Many studies have also examined the role of other niche cells, including endothelial cells (Gilbertson and Rich, 2007) and, more recently, even neurons (Venkatesh et al., 2017), in maintaining tumor cell survival and growth. The current work by Wang et al. adds to the complexity of these cellular interactions by demonstrating a key role for DGCs in tumor propagation. Despite this daunting complexity, the study also identifies a potential therapeutic target: the disruption of the DGC-GSC interaction via inhibition of the BDNF-NTRK-AKT-VGF axis. However, further investigation is required to determine whether the interaction between DGC and GSC occurs in the various flavors of GSC—such as ones at the edge and ones at the core of tumors. Furthermore, given that surgical resection removes the bulk of the tumor, and radiation and chemotherapy primarily kills DGCs, skewing the relative proportions of DGCs to GSCs and their interaction dynamics with the microenvironment, it will be worthwhile to discern if the BDNF-NTRK2-VGF circuit is employed by GSCs and DGCs in tumors that recur post-treatment—the cause of death in the majority of GBM patients.

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