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Engineering strategies to mimic the glioblastoma microenvironment ☆

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and deadly brain tumor, with a mean survival time of only 21 months. Despite the dramatic improvements in our understanding of GBM fueled by recent revolutions in molecular and systems biology, treatment advances for GBM have progressed inadequately slowly, which is due in part to the wide cellular and molecular heterogeneity both across tumors and within a single tumor. Thus, there is increasing clinical interest in targeting cell-extrinsic factors as way of slowing or halting the progression of GBM. These cell-extrinsic factors, collectively termed the microenvironment, include the extracellular matrix, blood vessels, stromal cells that surround tumor cells, and all associated soluble and scaffold-bound signals. In this review, we will first describe the regulation of GBM tumors by these microenvironmental factors. Next, we will discuss the various in vitro approaches that have been exploited to recapitulate and model the GBM tumor microenvironment in vitro. We conclude by identifying future challenges and opportunities in this field, including the development of microenvironmental platforms amenable to high-throughput discovery and screening. We anticipate that these ongoing efforts will prove to be valuable both as enabling tools for accelerating our understanding of microenvironmental regulation in GBM and as foundations for next-generation molecular screening platforms that may serve as a conceptual bridge between traditional reductionist systems and animal or clinical studies.

Contents

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1. Introduction

Glioblastoma multiforme (GBM) is the most common and deadly form of primary brain cancer, accounting for approximately 54% of all brain tumors in the United States [1]. Despite its prevalence and lethality, there is currently no definitive treatment for patients afflicted with GBM. This lack of treatments is often attributed to the diffuse and unrelenting infiltration of tumor cells throughout the brain, [2] a phenomenon famously observed by neurosurgeon Dr. Walter Dandy in the 1920s, when he took the extreme step of surgically removing entire brain hemispheres of two comatose patients afflicted with GBM, only to see the tumor return post-resection [3].

While current treatment options are significantly more sophisticated than those exercised by Dr. Dandy, patient outcomes still remain poor. Standard therapy consists of the combination of tumor removal through surgical resection, radiotherapy, and chemotherapy. Following resection, image-guided radiotherapy is typically applied to the tumor margins, often including concomitant treatment with the alkylating agent temozolomide (TMZ) [4]. Despite this aggressive treatment regimen, tumor recurrence at the margin of the resection occurs in approximately 90% of patients and mean survival time is only around 21 months [4,5]. One of the main difficulties in effectively treating GBM with conventional therapies is that tumors that appear similarly in histopathological presentation are often in fact quite distinct at the cellular and molecular levels. For example, recent genomic analysis of many patient-derived GBM samples revealed at least three distinct subtypes of GBM, each of which contains specific genomic lesions relative to matched normal brain tissue (Fig. 1) [6,7]. Furthermore, there is substantial cellular heterogeneity within a single tumor, with mounting evidence supporting the idea that tumor progression is driven by a subpopulation of glioma stem/initiating cells, which have high tumor-forming potential and express many neural stem cell markers [8]. Because cells in each tumor are distinct from other tumors classified as GBM, conventional treatments targeting intracellular signaling pathways, such as those regulating proliferation, will likely only be effective for a small subset of patients, and perhaps then only transiently as resistance evolves.

Motivated by these findings, recent clinical trials have begun to explore new directions in the treatment of GBM with the aim of targeting the few common features shared across GBM subtypes. Instead of targeting cell-intrinsic pathways, these trials seek to intervene by manipulating the extracellular environment and the interactions of tumor cells with this environment, which is beginning to be recognized as a critical regulator of tumor progression [9–11]. Important components of the microenvironment include: 1) the extracellular matrix (ECM), the biopolymeric scaffold surrounding tumor cells, 2) non-tumor cells near or within the tumor, such as astrocytes, macrophages, endothelial cells, and fibroblasts, and 3) soluble and scaffold-bound signals such as growth and differentiation factors. Particularly intriguing is treatment with anti-angiogenesis drugs such as bevacizumab, which targets vascular-endothelial growth factor (VEGF), thereby reducing tumor-induced vascular recruitment. Bevacizumab has been shown to increase progression-free survival in phase III clinical trials when added to a regimen of radio- and chemo-therapy, but does not significantly improve overall survival [12–15]. In another novel modality of GBM treatment, directing cell migration towards an external chemotherapeutic sink with an implanted, migration-promoting hydrogel

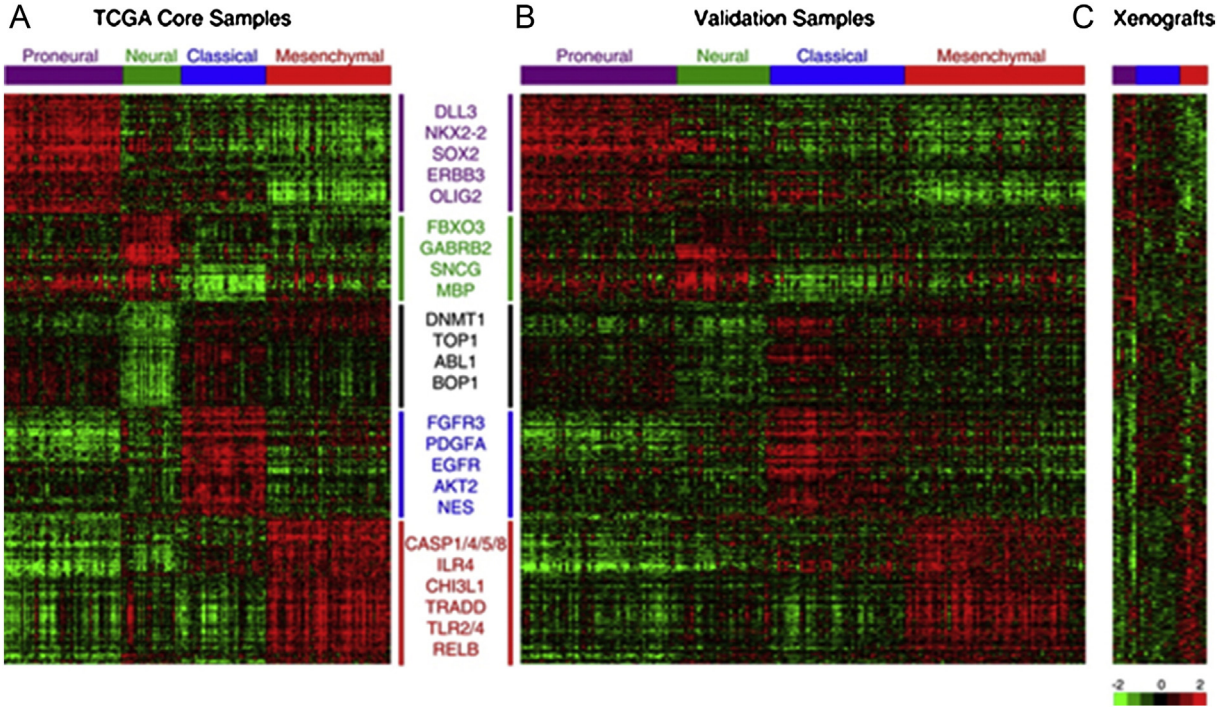

Fig. 1. Heterogeneity in GBM tumors. Hierarchical clustering of 200 tumors and 1740 genes revealed four distinct, statistically significant subtypes in GBM samples, which can be minimally represented by a predictive 840 gene sample (A). Red depicts genes that are overexpressed relative to normal tissue, while green depicts genes that are underexpressed. The four subtypes are named according to the lineage the tumor type most resembles. Performing the same analysis on either previously published data (B) or xenografts taken from mice (C) confirm the presence of four distinct subtypes. Figure adapted from Verhaak et al. (2010), with permission.

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