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Mini-review

Metabolic regulation of glioma stem-like cells in the tumor micro-environment

Tom M. Thomas [a, b, *], John S. Yu [a]

[a] Maxine-Dunitz Neurosurgical Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[b] Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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ABSTRACT

Cancer metabolism has emerged as one of the most interesting old ideas being revisited from a new perspective. In the early 20th century Otto Warburg declared metabolism the prime cause in a disease of many secondary causes, and this statement seems more prescient in view of modern expositions into the true nature of tumor evolution. As the complexity of tumor heterogeneity becomes more clear from a genetic perspective, it is important to consider the inevitably heterogeneous metabolic components of the tumor and the tumor microenvironment. High grade gliomas remain one of the most difficult to treat solid tumors, due in part to the highly vascularized nature of the tumor and the maintenance of more resistant stem-like subpopulations within the tumor. Maintenance of glioma stem cells (GSCs) requires specific alterations within the cells and the greater tumor microenvironment with regards to signaling and metabolism. Specific niches within gliomas help foster the survival of stem-like sub-populations of cells with high tumorigenicity and high metabolic plasticity. Understanding these maintenance pathways and the metabolic dependencies within the niche may highlight potential avenues of addressing tumor resistance and recurrence in glioma patients.

Introduction

Glioblastoma represents one of the most lethal solid tumors with one of the highest mortality rates, having an overall survival of approximately 12–14 months with the full complement of treatment [1]. Negligible progress has been made on that survival figure despite advancements in chemotherapy and surgical techniques over the past 30 years. This has required a reassessment of where within our understanding of glioma biology the major gaps in knowledge remain and the sobering reality is that the gaps are not small. The developing view of tumors as heterogeneous disease comprised of many subpopulations with unique properties has forced us to consider more closely the dynamics within a tumor that play a role in not only driving tumor development forward but also in maintaining tumor survival under severe stress. It is important to start to piece together the specifics of the many different networks within a tumor system including interactions between tumor subpopulations, interactions between the tumor and its stroma surrounding, interactions between the tumor and the immune components, and even interactions between the tumor and the local stem compartment. With the need to begin to address these gaps in understanding gliomagenesis, the tumor microenvironment and the complex metabolic networks within these tumors have come into particular focus in recent research.

Tumor metabolism fundamentally discusses two major points of cell behavior: (1) the specific sourcing of macromolecules of metabolites, and (2) the different cellular mechanism used to deal with different nutrients for either anabolic construction or catabolic breakdown. Many tumors have been shown to augment its microenvironment in order to more optimally acquire nutrients, which is of particular importance to solid tumors as the tumor core becomes more isolated from the native vascular infrastructure. Microvascular hyperplasia is one of the important hallmarks in glioma development and in fact most gliomas maintain extensive, proliferative vascular endothelium [2]. Although this vasculature is required for most of the tumor bulk, solid tumors will have variability in access to oxygen and nutrients in different tumor compartments, and adaptations to this variability is also important for tumor growth. As solid glioma bulk grows in mass, the core tumor space will begin to form necrotic and hypoxic regions and a

* Corresponding author. Department of Pathology, Toker Laboratory, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA.
E-mail address: tmthomas@bidmc.harvard.edu (T.M. Thomas).

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significant amount of necrotic buildup ensues. However, there will also be cellular compartments within the tumor bulk that adapt to the oxygen and glucose gradients and may thrive in this space. Within a single tumor one will find many different cellular compartments with variations in oxygenation and fuel source availability and there will be cells enriched in these compartments that have made the suitable adjustments to accommodate these conditions. This again harkens back to the complex heterogeneity of solid tumors which only gets worse with tumor progression. Furthermore, the body of research over the past decade regarding glioma stem-cell (GSC) populations have indicated certain highly resistant and tumorigenic sub-populations are maintained in specific microenvironmental niches, particularly enriched in these perinecrotic/hypoxic/perivascular compartments [3–5].

The cellular adaptations that allow for the development of tumor subpopulations is therefore something that not only requires more investigation but also constitutes one of the key elements to understanding cellular resistance and recurrence. Much of research over the past decade have looked at the source of tumor subpopulations and even tumor origin itself and has suggested the existence of tumor progenitors or tumor initiating stem-like populations in many cancers. The cancer stem cell (CSC) hypothesis as it has come to be known proposes that these stem-like subpopulations are maintained across a wide array of tumors and are predominantly aggressive cellular subsets that can be resistant to nutrient stresses as well as treatment stresses. These cancer stem populations maintain unrestricted self-renewal capacity and this allows for the propagation of the tumor even under insult of therapy [6]. GSCs share many of the same biological hallmarks of normal neural stem cells which includes the ability to form neurospheres, express neural stem markers, and differentiate into both astrocytic and neural lineages [6,7]. The most compelling reason to study glioma biology with GSCs is the fact that they have been shown to be very tumorigenic *in vivo* and form diffuse and invasive tumors that are highly resistant to conventional treatments, indicative of actual patient disease in clinic [8,9]. Therefore, the need to understand how GSCs are maintained and what, if any, contribution comes from the microenvironment is highly relevant. A key feature of many of these progenitor cell populations or cancer stem cells is the metabolic plasticity that has been described in the literature [10]. The ability to modulate key cellular metabolism processes to adapt to changing nutritional climates may in fact describe an important aspect to the resistance phenotype these cells display. Therefore, the metabolic requirements of these GSCs and their microenvironment are very important in understanding how resistance is established in these tumors.

Most cancer cells have been shown to rely on glycolysis instead of oxidative phosphorylation for glucose metabolism, as described by Warburg et al. [11]. The Warburg Effect has been a fixture of cancer cell biology for almost a decade now but new research has been able to describe many instances where the Warburg effect is either not observed or observed to only a certain degree [10]. This would make sense considering most tumors represent a mix of cellular pools that could have diverging metabolic requirements. In fact, there has been diverging observations regarding cancer stem cell metabolism across different tumors. GSCs have been reported to have distinctly different metabolic phenotypes compared to more differentiated tumor cells, and appears to be able to easily switch between glycolytic and oxidative metabolism depending on the microenvironment [12]. This suggests that despite differences in basal metabolism, cancer stem metabolism may rely more on the capacity for metabolic adaptability and reprogramming than on a primary metabolic profile across cancer.

This review will focus on the interactions between the tumor microenvironment and GSCs, specifically looking at the metabolic requirements and dependencies of both components. The relationship between GSCs and the specific stem compartments of the tumor and the vascular/hypoxic niches may shed light on an important element to maintaining these cells, and in turn maintaining the greater tumor.

Glioma stem cells

Through human development most cells in the body mature from stem-like precursors towards more differentiated cellular fates. These differentiation events are functionally important and tend to result in committed cellular steps towards terminal cell states. However, it is an important aspect of tissue homeostasis to maintain certain sub-populations of stem-like precursors that can give rise to functionally mature progeny in the event of cellular turnover or wound healing [13]. In cancer, it has been proposed that elements of this homeostatic mechanism have been hijacked for cancer propagation.

The original cancer stem cell (CSC) hypothesis proposed a model of tumor propagation via stem cell precursors using the hierarchical model of cell division. The traditional hierarchical model of cancer stem cells states distinct stem-like populations exist from the beginning of the tumors inception and are in fact responsible for the propagation of various more differentiated cell populations that will go on to make up the heterogeneous tumor pool [14,15]. In this model, treatment resistance is at least in part explained but the maintenance of the parental cancer stem cells which can then repopulate the tumor bulk once the treatment insult is removed. An alternative idea being developed with regards to cancer stem cell propagation posits the idea of clonal evolution, where the accumulation of a series of mutations, in time, will drive cells away from their assigned cell fates and slowly dedifferentiate into a more progenitor state. In theory, a tumor will eventually develop one or more distinct stem-like clonal populations that have recaptured self-renewal capacity that can then be implemented towards tumor survival and growth. In light of current understandings of tumor heterogeneity and tumor resistance/recurrence, it is more likely that both of these models may in fact describe different elements of a central process and therefore both explain the cancer stem cell model to a point, as some have proposed a hybrid of the two theories to explain the complex dynamics involved (Fig. 1) [13,16–18]. The important fact remains that however these cells may have come to be, the elimination of the cancer stem cell population in any tumor model represents one of the most important hurdles to cancer research and treatment today.

Glioma stem cells have been demonstrated *in vitro* to have self-renewal capacity, differentiate into multiple cell lineages, form neurospheres, and express specific neural stem cell markers such as Nestin, Sox2, Prom1/CD133, and Nanog. Several more markers have been suggested over the years and there is unlikely to be a specific expression profile that encompasses every stem-like glioma subpopulation [19,20]. GSCs have been shown to be more resistant to both chemotherapy and radiation above differentiated tumor cells and several studies have specifically shown GSC ability to repopulate a tumor and drive secondary tumor recurrence post-treatment [3,9,21–23]. To further confound things, as with tumors in general, there has been shown to be great heterogeneity even within the GSC pools, which is consistent with the models of CSC maintenance and propagation. Various different expression subtypes have been described in glioma patients (proneural, mesenchymal, classical, and neural) and several of these subtypes have also been attributed to GSCs as well (proneural and mesenchymal) [24]. Distinct GSCs clones even from the same tumor can display variability in gene expression profile and metabolic dependencies [25,26]. There is evidence to suggest that variability in GSC clones is at least in part