

Glioblastoma: Potential Role of Induced Pluripotent Stem Cells in Personalized Medicine

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ABSTRACT

In recent years great advances have occurred in the field of oncology. However, one cancer that is yet to be fully understood is glioblastoma, a highly aggressive Grade IV type of glioma. This lack of understanding is largely caused by the heterogeneity of glioblastoma which leads to differences in patient symptoms, difficulty in treatment with common approaches (like chemotherapy), and difficulty in the prognosis of the disease. In order to combat these challenges, scientists are turning to emerging new approaches, one of which is the utilization of induced pluripotent stem cells (iPSCs) to generate cerebral organoids that model aspects of the human brain environment. iPSC-derived cerebral organoids are distinct from patient-derived glioblastoma organoids, which are generated directly from tumor tissue, and from hybrid models that combine patient-derived tumor material with iPSC-derived cerebral organoids. These different experimental platforms may contribute to personalized glioblastoma research by allowing researchers to study tumor behavior, treatment response, and tumor interactions with surrounding brain tissue in different ways. Current studies, however, primarily demonstrate experimental disease modeling and drug-response testing rather than validated clinical decision-making. Further prospective validation, improved reproducibility, practical turnaround times, and stronger correlation between organoid responses and patient outcomes are needed before these approaches can be considered for routine clinical use.

INTRODUCTION

Glioblastoma is a highly aggressive Grade IV type of glioma (tumor that starts in glial cells in the brain) which affects the central nervous system. In recent years there are a lot of advances in cancer treatment however the prognosis for glioblastoma is very poor (1,2,3,4). The highly infiltrative nature of glioma into the surrounding normal brain tissues, the high rate of migration from the tumor core, and the ability to generate secondary microsatellite tumors in normal brain parenchyma are the major causes of poor prognosis in patients with GB. Traditional treatments for GB include surgical resection and chemoradiation therapy. However, since the removal of microsatellite tumors by surgery is not feasible, GB remains one of the most fatal forms of malignant primary brain tumors. Therefore, due to the varying conditions and attributes of the disease among patients in combination with the infeasibility of more traditional methods, scientists are turning to stem cells in order to learn more about the disease.

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Researchers are studying and exploring use of iPSCs-derived cerebral organoids to better mimic the human brain in a lab setting. Induced pluripotent stem cells derived cerebral organoids are made by reprogramming regular adult human cells such as blood or skin cells into iPSCs. Then the iPSCs are guided to develop and differentiate into a three-dimensional brain like structure that mimics aspects of the brain. The cerebral organoid thus formed is not a tumor. The cerebral organoid provides a control model of the human cerebral environment.

In contrast to iPSC derived cerebral organoids, patient derived glioblastoma organoids are generated directly from surgically resected tumor tissue. The tumor is divided into small fragments or dissociated into cells and maintained in three-dimensional culture, where the cells grow into tumor-like structures that can retain important characteristics of the patient's original glioblastoma (5).

In order to capture both the patient specific tumor and the surrounding brain environment, researchers have developed hybrid models that combine elements of both approaches. These hybrid models combine iPSC derived cerebral organoids with glioblastoma cells from patient or patient derived tumor tissue. This makes hybrid models particularly useful for studying tumor invasion and interactions between glioblastoma and normal neural tissue (6).

These different organoid approaches also have distinct roles in the development of personalized treatments for glioblastoma. Patient-derived glioblastoma organoids, for example, can be used to evaluate how an individual patient's tumor responds to a specific therapy. This can be seen in a study of chimeric antigen receptor (CAR)-T cells in glioblastoma, in which researchers tested CAR-T therapy using organoids generated directly from patients' tumor tissue (5). Importantly, these were patient-derived glioblastoma organoids rather than iPSC-derived cerebral organoids, demonstrating the potential of patient-derived tumor models for individualized treatment testing. iPSC-derived cerebral organoids and hybrid models, on the other hand, provide different advantages by allowing researchers to study the human brain environment and the interaction between glioblastoma and surrounding neural tissue. Together, these models may help researchers better understand the heterogeneity of glioblastoma and develop more individualized approaches to treatment. This literature review will discuss current treatment options for glioblastoma, explore the growing utilization of RNA sequencing data to better understand tumors, examine the use of iPSC-derived cerebral organoids, patient-derived glioblastoma organoids, and hybrid models in glioblastoma research, and discuss the advantages and disadvantages of these approaches and their potential role in addressing tumor heterogeneity in the future.

METHODS & MATERIALS

All of the research articles used in this review were obtained through PubMed, which is a well known database that contains peer-reviewed biomedical and life science research. The literature search was conducted in November 2025. Articles were searched using several keywords related to the topic,

including “glioblastoma,” “glioblastoma treatment,” “glioblastoma stem cells,” “induced pluripotent stem cells (iPSCs),” “tumor resistance,” and “glioblastoma therapy.” Different combinations of these keywords were used to locate studies that were most relevant to the focus of this review. The PubMed searches identified 75 potentially relevant articles, all of which underwent title and abstract screening.

To ensure that the information used was reliable and up to date, only peer-reviewed articles written in English and published within the 10-year search window from November 2015 through November 2025 were included. Preference was given to review papers, clinical studies, and experimental research that focused on treatment strategies, the biological behavior of glioblastoma tumors, or potential new approaches involving stem cells and organoid models.

The titles and abstracts of the articles were first reviewed to determine whether they were relevant to the topic. From the initial search results, 20 articles were selected for full-text review. If an article appeared relevant, the full text was then read thoroughly. Studies that specifically discussed treatment resistance, tumor biology, or emerging stem-cell-based therapies such as induced pluripotent stem cells were included in the review. Studies involving iPSC-derived cerebral organoids, patient-derived glioblastoma organoids, and hybrid organoid models were also evaluated according to the specific model used in each study. Articles that were not directly related to glioblastoma or that did not provide sufficient scientific information were excluded. After applying these inclusion and exclusion criteria, 11 peer-reviewed articles were ultimately included in the final review.

RESULTS

After going through the literature, one of the most apparent patterns was that glioblastoma is extremely difficult to treat because it does not behave the same way in every patient. Even though surgery, radiation, and chemotherapy are still the standard forms of treatment, the outcomes are often disappointing. A major reason for this is that glioblastoma is highly heterogeneous (2,4). This heterogeneity occurs at two levels. Intertumoral heterogeneity refers to biological differences between tumors from different patients, including differences in genetic alterations, gene-expression patterns, and tumor microenvironment. Intratumoral heterogeneity refers to the presence of multiple cellular and molecular states within different regions of the same tumor (2,4). Because of this, a treatment that works in one patient may not work nearly as well in another, and even within the same patient, some tumor cells may respond while others survive and continue to grow. Importantly, intratumoral heterogeneity also means that a tumor sample taken from one region may not contain every clinically relevant cellular population present elsewhere in the tumor. This helps explain why broad treatment approaches like chemotherapy often fall short. These findings provide a rationale for investigating more individualized approaches.

The literature also showed that researchers now have much better tools for studying glioblastoma than they did in the past. Newer techniques such as single-cell RNA sequencing, spatial transcriptomics, and other molecular profiling methods have made it possible to look at tumors in much greater detail. These

methods are important because they do not treat the tumor like one single mass. Instead, they allow scientists to look at the different cell populations inside it and see how they vary. This has helped researchers better understand intertumor heterogeneity, meaning the differences between tumors from different patients, as well as intratumor heterogeneity, which refers to differences within the same tumor (2,4). For example, Neftel et al. performed single-cell RNA sequencing on 28 glioblastomas and integrated these results with bulk genetic and expression data from 401 specimens from The Cancer Genome Atlas (TCGA) (2). The study identified four major malignant cellular states: neural-progenitor-like, oligodendrocyte-progenitor-like, astrocyte-like, and mesenchymal-like states. Individual tumors contained cells in multiple states, while the proportions of these states differed between tumors (2). Wang et al. similarly demonstrated that glioblastoma transcriptional subtypes can evolve over time and are associated with changes in immune components of the tumor microenvironment (4). Together, these findings help explain why different populations within the same tumor may respond differently to therapy.

At the same time, the literature made it clear that these advanced methods have limitations. Even though they can generate a huge amount of information, they do not automatically solve the treatment problem. In many cases, they tell researchers what is happening inside the tumor, but they do not directly tell doctors which therapy will work best for a particular patient. Another issue is that these methods can be expensive, technically demanding, and heavily dependent on data analysis. They are very powerful for understanding tumor biology, but they are not always practical as stand-alone tools for personalized treatment decisions. This is one reason why iPSC-derived cerebral organoids, patient-derived glioblastoma organoids, and hybrid organoid models are being explored as complementary tools in glioblastoma research (1,6,7,8).

Each of these models provides a different way to study the complexity of glioblastoma. Compared with traditional two-dimensional cell cultures, three-dimensional organoid systems can reproduce aspects of tissue architecture and cell-to-cell interaction that are difficult to model in monolayer cultures (1,8,9). Regular flat cell culture systems are useful for some experiments, but they often oversimplify the disease. Patient-derived glioblastoma organoids can retain important features of the source tumor, while iPSC-derived cerebral organoids can provide a brain-like environment in which tumor growth and invasion can be studied (1,5,8,9). However, even models established from patient tissue may not capture every cellular population present in the original tumor because the resected sample represents only part of a spatially heterogeneous tumor, and some cellular populations may be lost or selected against during culture (8,10).

Peng et al. developed a hybrid model termed an individualized patient tumor organoid (IPTO), in which surgically obtained patient tumor explants were cultured within iPSC-derived cerebral organoids (11). The resulting models preserved several histopathological, genomic, epigenomic, and cellular characteristics of the original tumors. The study also reported that IPTO responses to temozolomide were associated with patient-specific responses in a prospective cohort (11). This represents encouraging early evidence that organoid responses may correlate with clinical outcomes, but it does not by itself establish

organoid-guided therapy as a validated standard for clinical decision-making. Independent prospective validation and evidence that treatment decisions based on these models improve patient outcomes are still required.

This connects strongly to the idea of personalized medicine. Experimental organoid systems may eventually provide functional information that complements molecular profiling by showing how an individual tumor responds to treatments in vitro. Ratliff et al., for example, established patient-derived glioblastoma organoids from recurrent tumors and tested a panel of 41 FDA-approved drugs (7). Potential treatment options were identified for three of four patient tumors, with reported turnaround times of 13–15 days for those cases (7). This study demonstrated the feasibility of patient-specific drug-response testing within a potentially relevant time frame, but it was a small proof-of-concept study rather than evidence that organoid-selected treatments improve survival or other clinical outcomes. Therefore, these systems currently appear more appropriately described as experimental or preclinical platforms with potential future applications in personalized medicine rather than established clinical tools.

Although the research on organoid models is promising, the literature also points out several drawbacks that should not be ignored. For iPSC-derived cerebral organoids, generating iPSCs and differentiating them into reliable brain models is not simple. It takes time, technical skill, and carefully controlled lab conditions. This may limit how quickly these methods can be used in real clinical settings, especially for aggressive diseases like glioblastoma where treatment decisions often need to be made quickly. Another issue is that iPSC-derived cerebral organoids do not always perfectly represent mature adult brain tissue. In some cases, they resemble earlier developmental stages more than the fully developed brain. That can be a problem when the goal is to model an adult brain tumor as accurately as possible. There are also concerns about reproducibility, since results can vary depending on the protocol, the lab, or even the cell line being used. Cost is another barrier, and there are still questions about how easily these systems could be scaled up for routine patient care (1,8,10). In addition, these models do not fully reproduce the tumor microenvironment, particularly its vascular and immune components (1,8,10).

Patient-derived glioblastoma organoids have a different set of limitations. Their success can depend on the quality, amount, and composition of the surgically resected tumor tissue. Because only part of a heterogeneous tumor is sampled, the resulting organoid may not contain every cellular population present in the patient's tumor. During longer periods of culture, immune cells and other components of the original tumor microenvironment may also decrease or be lost (8,10). These changes can affect how accurately the model represents tumor behavior and treatment response.

Hybrid models address some of these problems by combining patient-derived tumor material with cerebral organoids, providing surrounding neural tissue in which tumor invasion can be studied (6,8). However, these models are also more technically complex and still do not fully recreate the vascular, immune, and other components of the human tumor microenvironment (6,8). Because vascular, immune, and other microenvironmental components influence tumor growth, invasion, drug penetration, and

treatment response, their incomplete representation may affect how accurately these models reproduce what occurs in a patient.

DISCUSSION

After looking through the studies, it appears as though the potential role of iPSCs in personalized glioblastoma medicine is likely to be complementary rather than stand-alone. Rather than depending on one method, progress may come from combining molecular analysis with different organoid approaches. Sequencing and molecular profiling can be used first to identify major mutations, pathways, and cell populations in a tumor. Different organoid models can then provide functional information that complements these molecular findings. That combination seems more realistic than expecting either sequencing alone or different organoids alone to solve the problem (5,10).

The reviewed drug-response studies provide encouraging evidence for personalized applications, but the strength of that evidence should be interpreted carefully. Ratliff et al. demonstrated individualized drug-response testing using patient-derived glioblastoma organoids, while Peng et al. reported that treatment responses in a hybrid IPTO model were associated with patient responses to temozolomide (7,11). Together, these studies show that organoid models can be used experimentally to evaluate treatment response and, in some cases, that those responses may correspond with what is observed in patients. However, this is different from showing that organoid-guided treatment decisions improve patient outcomes. At present, these models are therefore better viewed as experimental tools that may complement molecular and clinical information rather than replace clinical decision-making.

Moreover, cost and practicality will matter a lot in deciding whether this kind of personalized medicine can actually become common in the future. Clinical translation will also require larger prospective studies showing that organoid responses are reproducible, can be obtained within a useful treatment window, and reliably correlate with patient outcomes (7,8,10,11). Over time, if researchers are able to make the process faster, cheaper, and more standardized, then broader use might become possible. So the future of this field probably depends not only on whether the science is promising, but also on whether the process can fit into real hospital workflows (10). Addressing these practical and clinical challenges will ultimately determine how large a role these experimental models can play in personalized glioblastoma medicine.

CONCLUSION

After looking at the research, it seems clear that glioblastoma is so hard to treat because it is not a simple or uniform disease. The most important takeaway from this review is that glioblastoma will probably not be managed well with a one-size-fits-all approach. The studies reviewed suggest that iPSC-derived cerebral organoids, patient-derived glioblastoma organoids, and hybrid models each offer different experimental ways to study this complexity of glioblastoma. In particular, the potential role of iPSCs may

be strongest when iPSC-derived cerebral organoids are used alongside patient-derived tumor models and molecular profiling rather than as a stand-alone personalized treatment approach.

Looking ahead, the future of personalized glioblastoma research may involve combining detailed molecular analysis with these different organoid approaches. At present, however, these models are promising experimental platforms rather than established tools for choosing treatment. Before routine clinical use, larger prospective studies are needed to confirm reproducibility, practical turnaround times, and whether organoid treatment responses reliably correlate with patient outcomes. If these challenges can be addressed, these approaches may eventually contribute to more individualized glioblastoma treatment.

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