



How do Glioblastoma Stem Cells Manipulate the Immune System to Benefit Tumor Growth?

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ABSTRACT

Brain tumors are difficult cancers to treat because of their aggressiveness, intratumoral heterogeneity, and resistance to therapy. Glioblastomas (GBM) are the most aggressive and deadly brain tumors in adults. Although there have been advances in surgery, radiation, and chemotherapy, the survival rates are still low which highlights the need for different approaches to therapies. Glioblastoma stem cells (GSCs) initiate growth, drive recurrence, and therapeutic resistance. These cells play an active role in shaping the tumor's immune microenvironment. Here, we will discuss the way GSCs interact and manipulate the immune system in this review article. The suppression of anti-tumor responses, immune evasive signaling, and progression are all key factors in the intensity of GBM. It is important to understand these processes because they can help to inform better and more effective therapies for GBM. This paper reviews the major ways glioblastoma stem cells suppress immune responses, including immune cell reprogramming, epigenetic silencing, and inhibition of immunotherapy.

Keywords: Glioblastoma, Glioblastoma Stem Cell, Epigenetics, Immunotherapy, Reprogramming

INTRODUCTION

Clinical Burden of GBM

Glioblastomas (GBM) are one of the most aggressive and common brain tumors in adults. GBM is a malignant tumor that is classified as a World Health Organization grade 4 astrocytic tumor. GBM comes from glial cells and is characterized by rapid proliferation, necrosis, microvascular growth, and spread and infiltration into surrounding brain tissue. Glial cells are non-neuronal support cells in the nervous system and are essential for brain functioning. According to the SEER Cancer Statistics from 2022, malignant brain and other nervous system tumors (which include glioblastomas) for all ages have a mortality rate of about 4.4 deaths per 100,000 people annually in the United States (SEER*Explorer Application, 2022). Therefore, to better understand why glioblastomas are so difficult to treat, this paper will focus on the roles of glioblastoma stem cells in tumor growth, resistance, and aggressiveness.



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Demographics

Glioblastomas are typically diagnosed in older people, particularly men, and show higher occurrence among non-Hispanic, White populations. Incidence in males from 2000-2023 typically ranges from 3.9 cases per 100,000, which is much higher compared to women who have around 2.3-2.5 cases per 100,000 (SEER*Explorer Application, 2022). The tumor's aggressiveness stems from its high intratumoral heterogeneity, its ability to develop resistance to therapy, and the protective barriers of the brain, including the blood-brain barrier and immunosuppressive tumor microenvironment. These factors make GBM extremely difficult to treat compared to other brain tumors. Even though there are many aggressive treatment options like surgery, radiation, and chemotherapy, the median range of survival is only up to 12–15 months, with less than 10% of patients surviving five years after diagnosis (SEER*Explorer Application, 2022).

Prognosis & Treatment options

Knowing the clinical burden and demographics of GBM, it is also important to look into current treatment options and why they often fail in improving patient survival. Most current treatment options for GBM have changed very little in the past 20 years. The standard of care for patients with GBM involves surgical resection of the tumor followed by radiotherapy and temozolomide chemotherapy. Temozolomide therapy is a chemotherapy drug that is essential in the treatment process for glioblastomas. It is an oral alkylating agent, and it works by adding an alkyl chemical functional group to DNA, inducing DNA damage, leading to cell death in quickly dividing cancer cells (Dresemann, 2010). However, about 83% of the time, the glioblastoma patients relapse within a year (Faustino et al., 2020). The tumor location, spread, and infiltration within important brain regions can also limit surgical success. After surgical resection and chemotherapy treatment, residual resistant glioblastoma stem cells can continue to proliferate and cause relapse. Immunotherapies, including immune checkpoint inhibitors, CAR-T cells, and different peptide vaccines, have been tested but have not demonstrated direct clinical benefits or improvements in survival of glioblastoma patients (Liu et al., 2024). This is mostly due to tumor antigen heterogeneity, T cell exhaustion, and the immunosuppressive tumor niche. Newer approaches, such as Tumor Treating Fields, oncolytic viruses, and novel drug combinations,

have shown some benefit with small improvements, but there is still no result that has achieved a significant long-term effect.

Tumor Treating Fields (TTFields) are a non-invasive device-based therapy that uses low-intensity alternating electric fields to disrupt mitosis. A main limitation of TTFields is that it is not curative for GBM. Its effective duration is short, and recurrence of GBM still occurs, which leads to the long-term benefit of TTFields in question. Additionally, oncolytic viruses are built to infect and kill selected tumor cells and stimulate anti-tumor responses; however, there is no clear outcome on the effectiveness of this strategy. Early phases of oncolytic therapies have been reported to have a median survival outcome of around 12.5 months (Coates et al., 2025). It is noteworthy that the one-year survival rate averages from around 40-50%, showing that the oncolytic therapies are also not effective in the long term. Lastly, scientists continue to test investigational drugs and combinations with some early outcomes, but no final, clear improvements have been made yet. Therefore, GBM remains a uniquely aggressive cancer, defined by its resistance to treatment and poor prognosis despite decades of research.

Role of Glioblastoma Stem Cells

It is essential to understand why these treatments are ineffective, and we need to look into the backbone of GBM's aggressiveness: glioblastoma stem cells. Glioblastoma stem cells (GSCs) are a type of cancer stem cell and have the ability to regrow the tumor even after treatment. GSCs can also withstand therapies through alternative DNA repair pathways, adaptive drug resistance, and suppression of apoptosis (Eckerdt and Platanius, 2023). GBMs are a highly resistant tumor that frequently reoccurs even after treatments, partly due to glioma stem cells that can survive chemotherapy and promote malignant growth (Auffinger et al., 2015).

Immune Privilege of the Central Nervous System

The immune system of the brain functions differently from the immune system of the rest of the body. The brain is protected by the blood-brain barrier, which carefully regulates what can enter through the bloodstream. Harmful pathogens that try to enter can be blocked by the brain's barrier, but that also makes it harder for helpful immune cells or therapies to enter the brain and do their job. While the rest of the body

typically depends on the circulating immune cells, the brain relies on resident cells like microglia and astrocytes to function. These are two types of glial cells that support the central nervous system. Microglia are phagocytic and remove waste. Microglia are immune cells that continue to examine the environment for signs of infections, diseases, and injuries in the brain and activate responses. Astrocytes are star-shaped cells that provide structural support and maintain the blood-brain barrier, and regulate blood flow. On its own, astrocytes are very crucial in the immune system of the brain; however, when there is a glioblastoma in the brain, things can change. These glioblastomas can reprogram the microglia and astrocytes to make them support tumor growth. As a result, an immunosuppressive microenvironment develops to protect the tumor from the body's natural immunity (Chen et al., 2025; Jiang and Li, 2025; Lin et al., 2024).

Discussion

Mechanisms of Immune Manipulation by GSCs

Glioblastoma stem cells (GSCs) are a small subpopulation but play an essential role in glioblastomas (GBMs), contributing to the tumor's aggressiveness and resistance. These cells portray typical cancer stem cell traits including the ability to reproduce themselves, their ability to evolve into other tumor cells, and build a new tumor. Studies show that GSCs are mainly found in specialized places like perivascular and hypoxic regions, where the environment in those regions benefits their survival and maintains their stem-like traits (Tang et al., 2025; Wang et al., 2021). These points where the GSCs are found also protect them from treatment. For instance, hypoxia, a condition where there is low oxygen availability, can reduce radiation efficacy and select for therapy-resistant GSCs. Because GSCs can initiate the tumor again after therapy, they are a primary reason for GBM's recurrence following aggressive treatments such as surgery, chemotherapy, and radiation (Rodriguez et al., 2022). The literature consistently supports the general idea that GSCs are critical for tumor initiation and maintaining glioblastomas. GSCs can rapidly adapt to therapeutic stress, regenerate tumors, and reprogram immune cells to support GSC growth. GSCs communicate with other immune cells and stromal cells, which are structural cells that support the tumor. GSCs send out messages through cytokines, growth factors, and exosomes which weaken the immune activity and allow more

angiogenesis, which is the growth of blood vessels that support the tumor's health (Johnson et al., 2022). Targeting these survival mechanisms can therefore represent a promising therapeutic strategy to inhibit or prevent GBM recurrence.

There are many therapies being studied that target the survival mechanisms and the immune-evasion strategies GBM uses. One kind of therapy includes the chimeric antigen receptors (CAR) T cell therapies, where a patient's T cells are genetically built to recognize specific antigens that are part of tumors on GSCs and kill them. However, this kind of therapy is still under study because immunosuppressive tumor environments and other factors cause an impact to the T cells effectiveness (Zhou et al., 2025). Similarly, immune checkpoint inhibitors, like *PD-1* blockers, are being tested currently to remove the inhibitory signals on cytotoxic T cells, which allows the immune cells to better identify tumor antigens (Shen et al., 2020). Another example includes a clinical trial currently going on, where particular vaccines are designed to stimulate an immune response against certain GBM antigens, but certain combinations are still being tested.

Immune Cell Reprogramming

Glioblastomas and glioblastoma stem cells have developed mechanisms to avoid being detected and use the brain's immune system against it. Typically, microglia, resident cells of the brain, can detect any problems and get rid of any damaged or unknown cells, but in GBM, they end up being reprogrammed into a supporting tumor cell. Studies have shown that GSCs release signaling molecules that can suppress microglial activity, leading them to support tumor growth rather than supporting the brain's immune system (Chen et al., 2025; Sahoo et al., 2024). This interaction keeps repeating in a cycle, but in a way that continues to promote tumor growth. The tumor reprograms the microglia into helping it by allowing more invasion, avoiding the actual immune system, and promoting new blood vessel growth. GBM also has a huge benefit because the brain has natural immune limitations, such as restricted T cell entry, the blood-brain barrier, and low antigen presentation (Lin et al., 2024). All of these factors work together to create a place where GSCs can expand at a rapid pace and stay healthy. Understanding the communication methods of GSCs and microglia is crucial in order to develop new therapy options. Reprogramming the signals that GSCs

send out to microglia can reduce the resistance of GSCs to treatment.

Epigenetic Silencing

Beyond immune cell reprogramming, GSCs also evade immunity through epigenetic mechanisms. Glioblastoma stem cells can evade the immune system's response through epigenetic mechanisms, which are chemical changes that control gene activity without altering DNA sequence. A specific type of epigenetic change, called histone modification, can alter DNA packing by compacting chromatin and disrupting its organization, blocking the expression of important immune genes. They use epigenetic changes to turn off immune responses to make it look like they aren't there. Specifically, DNA methylation is what turns off the immune genes, which also includes the genes that help the immune system identify any cancer cells (Safa et al., 2015). This makes it hard for T cells to recognize the tumor and fight against it. It is shown in studies that GSCs use this to hide from the immune system (Sesé et al., 2022). These studies show that epigenetic changes are important since they connect the traits of the stem cells to more than just tumor growth, including immune evasion. However, these epigenetic changes have the ability to be reversed. There are certain drugs that can be taken such as DNA methyltransferase inhibitors or histone deacetylase inhibitors, that can turn the genes that were turned off before back on (Jiang and Li, 2025). This will make the tumor visible again to the immune system so that it can kick in and fight against the tumor (Safa et al., 2015). The ability to reverse the genes that were turned off can give scientists a chance to allow immune therapies to work better. Focusing on these epigenetic changes and targeting them can help advance the path of therapeutic improvement.

Implications for Immunotherapy

There have been many immunotherapies already looked at for glioblastomas. Some of these therapies include immune checkpoint inhibitors, CAR T cell therapy, and tumor vaccines. To test these immunotherapies, there have been clinical trials put in place, but the success rate has been limited. CAR T cell therapies have had higher rates of survival in the beginning, but then problems occur later on, including poor infiltration and persistence in the brain. As the tumor continued to be persistent, it ended up exhausting the CAR T cell therapy from working (Agosti et al., 2023). Additionally, tumor vaccines are

able to activate the immune system to try to attack or just target the tumor, but in the end, they haven't benefited many patients because of the tumor's ability to shut off the immune system again. The GBM's environment makes it hard for the immune system to function effectively because it is very restraining, different, and unique. A key factor is that the tumor would be secured by the blood-brain barrier system, which won't allow immune cells to enter. GSCs continuously make these issues even worse since GSCs can hide from the immune system, use epigenetic changes to turn off immune genes, and bring in cells that end up stopping immunity from helping (Zhou et al., 2025). These studies all show that the fact that immunotherapies have repeatedly failed in stopping the growth of GBM shows that the real focus should be on how GSCs avoid the immune system. Targeting these characteristics from the GSCs will help find lasting results from immunotherapies.

Exosomes and Regulatory T Cells

Going further than just epigenetic silencing, where the GSCs turn off the immune genes, GSCs also have some smaller techniques that limit the immune activity. They have the ability to also bring in regulatory T cells into the tumor environment, which suppresses immune activity and the immune system's response while also stopping the T cells from attacking the tumor. GSCs release small, tiny particles called exosomes, which carry microRNAs that can halt and completely shut off immune cells since they are used for cell communication (Johnson et al., 2022; Tang et al., 2025). Additionally, another way they evade the immune system is by modifying their own metabolism, where they use more sugar and break down specific amino acids, which creates a rough environment so that the immune cells can't do their job. When GSCs use large amounts of sugar and rapidly break down amino acids, it essentially restricts the nutrient availability and alters the surrounding microenvironment around them, damaging immune cell function and survival. These studies are well established in showing that these other ways really focus on how GSCs have many different pathways to succeed in immune evasion, more than what is already highlighted in most current therapies. More research into these moderations which include attracting regulatory T cells, suppressive exosomes, and metabolic reprogramming, can create new targets for new therapies to be created, which can possibly lead to one that works in suppressing GBM.

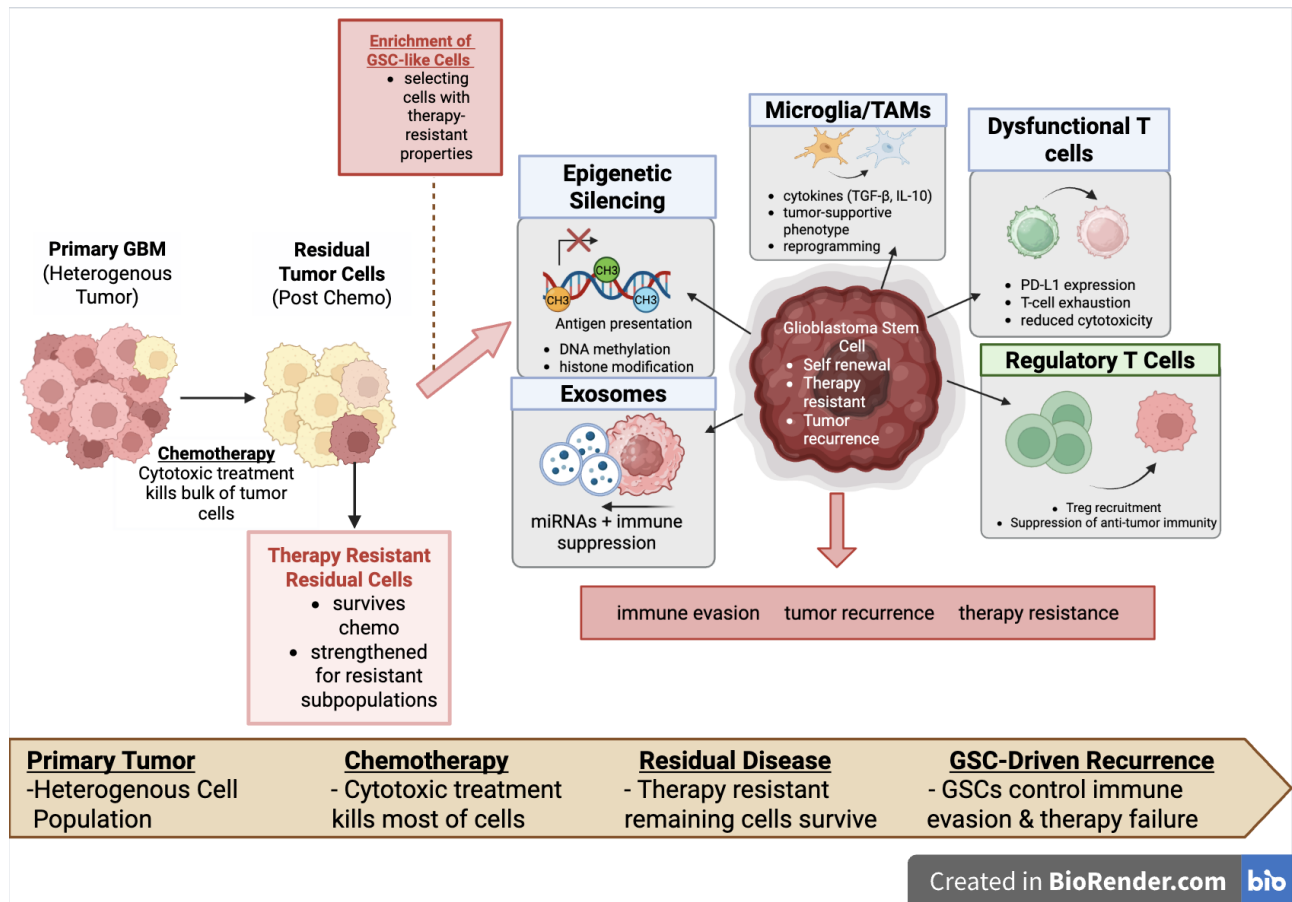


Figure 1. Glioblastoma stem cell immune manipulation infographic.

Primary glioblastomas include heterogeneous populations of cancer cells, and when treated with chemotherapy, most tumor cells are eradicated. However, some remaining cells are left behind, which are known as therapy-resistant cells. They are enhanced with stem-like properties and are called glioblastoma stem cells (GSCs). GSCs have various properties that work together to increase tumor development and treatment resistance. First, epigenetic silencing through DNA methylation and histone modifications occurs to reduce antigen presentation. Additionally, interactions with microglia and tumor-associated macrophages (TAMs) in the tumor microenvironment through cytokines like TGF-β and IL-10 advance a tumor-supportive phenotype. Initiation of dysfunctional T cells, as evidenced by abnormal

CONCLUSION

In conclusion, the way glioblastoma stem cells manipulate the immune system is what leads to tumor growth, immune evasion, and therapy resistance. Research studies consistently show how GSCs have an ongoing tendency to suppress anti-tumor immunity by secreting immunosuppressive cytokines, expressing immune checkpoint molecules, and reprogramming surrounding immune cells such as tumor-associated macrophages and regulatory T cells (Jiang and Li, 2025; Lin et al., 2024; Tang et al., 2025). Instead of avoiding immune detection, GSCs continue to function as the main regulators of the tumor's microenvironment (Sesé et al., 2022). This creates

many different kinds of conditions where general inflammation occurs while also preventing effective immune responses. These continuous patterns highlight the importance of GSCs in limiting glioblastoma progression and therapies failing.

However, multiple limitations come into play that prevent a definitive resolution to this issue. First, various studies provide evidence from animal models or lab dishes, which is vastly simplified in comparison to the complexity of natural human malignancies (Majc et al., 2021). Consequently, different cell types and immune system variations cannot be observable, which results in contradicting conclusions about the significance of specific immune signaling pathways.

The adaptability of GSCs and the changing environment of the tumor continue to make treatments with one pathway ineffective (Eckerdt and Platanias, 2023). Some future research should aim to include the human immune system, even when examining GBM with the use of animal models (Takei et al., 2025). In addition to that, efforts to develop therapies that degrade both GSCs and immune suppression build another crucial area of future investigation. With new and developed therapies as well as a stronger understanding of the connections between cancer stem cells and the immune system, significant outcomes to enhance the survival percentages of cancer patients can happen (Takei et al., 2025). By showing how GSCs actively interfere with the immune system, this research demonstrates how improving the understanding of certain interactions between the immune system and cancer cells could be an important step in creating lasting treatment strategies.

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Conflict of interest

The authors declare no competing interests.

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