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Glioblastoma Multiforme: The Role of Hypoxic Microenvironments in Glioblastoma Multiforme Tumors

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ABSTRACT

Glioblastoma Multiforme (GBM) is a high-grade glioma and one of the most aggressive tumor types within the central nervous system. Extensive research has explored the role of the tumor microenvironment in GBM progression, revealing diverse interactions and pathways that drive its development. A significant focus has been on hypoxic microenvironments, which are common in GBM and contribute to its immunosuppressive nature. The high heterogeneity and immunosuppressive characteristics of GBM present challenges for treatment, often reducing the efficacy of traditional therapies like chemotherapy and radiation. As a result, there is increasing interest in combination therapies as a more effective strategy for managing this aggressive cancer. This paper focuses on exploring research conducted on understanding the role hypoxic microenvironments play in GBMs persistence.

Introduction

Neurological tumors result from various mutations in their pathways, followed by serious health issues for patients. These can include astrocytoma, glioblastoma multiforme (GBM), meningioma, and many others. GBMs, or high-grade gliomas, are one of the most aggressive tumor types in the central nervous system [Park 2022]. GBMs are further exacerbated by hypoxic environments. Hypoxia results from an inadequate supply of oxygen in the tissue. It is the most critical factor that determines the prognosis of patients with GBM, as it promotes resistance to drug and other cancer therapy. Additionally, it is responsible for the inhibition of the immune responses. Though the brain requires the highest amount of oxygen, brain tumor regions are mostly hypoxic as the amount of oxygen is being compromised [Park 2022]. Since oxygen is a vital component of many metabolic processes, hypoxia has a large effect on tumors, including triggering glioma cell invasion, the process by which glioma cells spread into the brain's surrounding tissue [Tamai 2022]. The combination of therapy resistance and immune response inhibition leaves high-grade glioma extremely difficult to treat, resulting in heavy research on the causes and effects of GBMs.

Currently, there are limited treatments that allow for efficient removal of the tumor, including immunotherapy, chemotherapy, and radiation therapy. These treatments are inadequate and ineffective due to certain characteristics of GBMs such as its high immunosuppression abilities [Park 2022]. In such cases, we speculate that combination therapy may be highly effective in targeting multiple receptors of the tumor to reduce the spread and increase removal of the tumor. The synergistic effects of combination therapy may also allow for less therapeutic resistance. Additionally, targeting the hypoxic microenvironment may enable greater specificity for tumor removal.

Methods

Relevant literature and data were primarily gathered using PubMed as the main database, with a focus on GBM and its hypoxic microenvironment. Articles were screened for relevance to key areas: GBM progression, hypoxic and immunosuppressive microenvironment characteristics, microenvironmental interactions, and current or emerging therapeutic strategies, especially combination therapies. Selected studies were further evaluated to identify those contributing novel insights or adding to foundational knowledge. Data from each study were synthesized to provide an overview of current understanding, identify knowledge gaps, and highlight potential directions for understanding GBM's hypoxic microenvironments.

Gliomas

Gliomas are one of the most common types of brain tumors and have an extremely invasive nature [Tamai 2022]. This, along with their associated poor prognosis, extends across all both forms of gliomas, low (LGG) and high grade (HGG). LGGs often occur in younger patients who have a history of good health [Forst 2014]. LGGs consist of grade I and II tumors, and have a higher survivability compared to HGGs, which are typically more intense in nature, having heavier characteristics such as more mitotic activity than LGGs. In contrast, HGGs include grade III and IV gliomas, and have greater tumor heterogeneity, differences between the same type of tumors in different patients, or between cancer cells of the same tumor. It is important to note that currently, the grade of the tumor can only be determined through histopathologic examination of tissue, as only imaging does not reveal clear results [Forst 2014].

Treatments for patients with LGGs compared to HGGs are vastly different. Although chemotherapy is commonly used to treat HGGs, further research is needed to evaluate its efficacy in patients with LGGs due to the uncertain survival benefits it provides in these cases. [Forst 2014]. To determine the optimal treatment approach for patients with LGG, the potential benefits and side effects of each option must be carefully evaluated. Given that treatment side effects can significantly impact a patient's long-term quality of life, these risks must be weighed against the potential therapeutic benefits [Forst 2014]. It is important to consider the cognitive impact on patients, as brain-targeted treatments can lead to a range of effects on cognitive function.

GBMs are an HGG that is known to be one of the most aggressive and hypoxic tumor types in the CNS. GBMs heavily affects invasiveness, resistance to drugs, and antitumor immune responses. GBMs are classified as a "cold tumor," and recently developed immunotherapies are ineffective against GBMs. A "cold tumor" is a tumor that is not likely to trigger a large immune response, therefore preventing the body's ability to fight off the tumor. In combination with its "cold tumor" classification, GBMs have a large infiltration capacity, as tumor cells spread across the body easily. It is difficult to prevent all mechanisms and pathways due to its multi-step pathways and different signaling molecules of glioma invasion, rendering GBM hard to treat.

Hypoxic Microenvironments

Tumor microenvironments comprise a system of molecules, cells, and blood vessels that allow tumor cells to live. There is a clear lactic acid accumulation in tumor microenvironments that leads to a low pH. This inhibits antitumor immune response, allowing the tumor microenvironment to favor tumor progression [Park 2022]. Tumor infiltration into healthy tissue is driven by the interactions between glioblastoma cells and their surrounding tumor microenvironment [Erices 2023]. This interaction involves several different types of cells, including glia and stem-like cells, which interact with different microenvironment. GBM tumors can change their microenvironment depending on what fits their needs the best. This adaptability allows for greater invasiveness as well as resistance to treatments [Erices 2023]. This makes GBMs challenging to treat and highlights the need for developing innovative therapeutic strategies.

The tumor microenvironment plays a significant role in promoting angiogenesis, the growth of blood vessels, which can lead to the formation of dysfunctional vessels and induce hypoxia [Park 2022]. Hypoxia occurs when there is insufficient oxygen in tissues to maintain homeostasis, leading to the activation of transcription factors that enhance the tumor's invasiveness. Low oxygen conditions inhibit various processes, including hydroxylation, and can be readily maintained by the tumor [Erices 2023].

In addition to hypoxia, treatments such as surgery, chemotherapy, and radiation therapy further alter the microenvironment, enabling glioma cells to invade more readily [Tamai 2022]. Hypoxic microenvironments not only facilitate the invasion of GBMs, but also reprogram tumor cells through multiple pathways, contributing to significant tumor cell heterogeneity. This heterogeneity, along with the presence of hypoxia, renders many GBMs resistant to conventional cancer therapies. The diverse signaling pathways and molecules involved in the heterogeneity of GBMs, particularly in high-grade tumors, complicate treatment strategies and underscore the need for innovative therapeutic approaches.

GBM's hypoxic microenvironment is due to the association between GBM's aggressiveness and regional chronic cerebral hypoxia [Nicholson 2024]. It has been discovered that the exposure of cerebral organoids (COs) to chronic hypoxia increases stress on levels of oxygen. COs are 3D structures that are derived from pluripotent stem cells that mimic the structure and composition of the brain [Nicholson 2024]. Regarding the hypoxic microenvironment, local hypoxia also triggers cell migration, allowing tumor cells to spread and attack throughout the body. Hypoxia-inducible factor (HIF 1-alpha) promotes transcription of various invasion related molecules, allowing them to grow and spread. These factors are upregulated in tumor cells under a hypoxic microenvironment [Tamai 2022].

Hypoxia promotes immunosuppression within the GBM microenvironment through its reprogramming of glioma tumor cells [Park 2022]. Different proteins, such as HIF 1-alpha, induce the release of pro-inflammatory responses, which leads to an immunosuppressive phenotype. Immune cells need proper oxygen levels for survival and function. Hypoxia has shown to affect multiple functions of anti-cancer immune cells, promoting tumor growth instead and allowing it to invade further [Park 2022].

In hypoxic microenvironments, there is an increase in stem cell-like characteristics [Pantazopoulou 2021]. This increase causes more resistance to treatments and cancer therapies. Astrocytes, neural stem cells and a major component of the GBM microenvironment is an example of this. These stem cells become reactive in response to hypoxia, which feeds and facilitates the spread and invasion of gliomas; in particular, high-grade gliomas are most affected by this. Hypoxia astrocytes are able to remodel the tumor environment as they are involved in the tumor's growth, allowing for the further invasion of tumor cells [Pantazopoulou 2021].

Therapeutics

Due to GBMs being an aggressive brain tumor with high rate of recurrence, there are multiple unique treatment limitations. There is a relationship between the disease's poor prognosis and its resistance to current therapeutic approaches [Ghosh 2018]. Even after surgery as well as radiotherapy and chemotherapy, the tumor may continue growing [McBain 2021]. The weakened responses associated with radiation and chemotherapy results from inadequate cell targeting, resulting in healthy cells receiving treatment instead [Ghosh 2018]. Long-term effects of radiation therapy may also destroy normal cerebral microvessels, inducing areas of hypoxia [Nicholson 2024]. New approaches are being developed to overcome these limitations [Ghosh 2018].

In hopes that combinations of various drugs and treatment approaches would serve to be better for the future of treatment for GBMs, combination therapy has become a more popular approach that is currently being developed. Combination therapy works in an additive manner [Ghosh 2018]. This approach requires smaller drug doses, as it targets multiple pathways. In utilizing smaller doses, the issue of drug resistance to GBM tumor cells is also reduced through this process. Although combination therapy is effective at managing GBMs, there are still limitations due to the inadequate amount of research that has been done. Combination therapy may result in unwanted side effects on the patient, including high systematic toxicity, ulcers, and toxic DNA damage [Ghosh 2018]. More research needed

to find synergistic interactions between the current different treatment types including chemotherapy, radiation therapy, immunotherapy. More clinical testing would also for maximum effectiveness and results for the patient.

Discussion

The complex characteristics of GBMs cause substantial challenges for understanding their progression, as well as for developing effective treatment strategies. The effects of multiple current therapeutic options reveal the limitations of GBM's present-day treatments, of which has low effectiveness due to GBM's high tumor heterogeneity and other characteristics. Moreover, the tumor's hypoxic microenvironment and its characteristically high immunosuppressive qualities further affects GBM treatment outcomes, showing the need for better treatment discussion and options.

Both the immunosuppressive as well as hypoxic characteristics of the GBM microenvironment represent obstacles that cause therapies to be less effective. Due to GBM's classification as "cold tumors" that have limited immune response activity, immunotherapies are therefore less effective against them. The hypoxic factor then can reprogram immune cells, which leads to immune evasion. Based on this, there is a strong need for therapies that target the reprogramming of the tumor microenvironment to combat these characteristics.

In line with past research, standard therapeutic options such as immunotherapy, radiation, and chemotherapy prove to be often ineffective due to GBM's quick recurrence and drug resistance qualities. It has been shown that even after multiple therapeutic trials, GBM still continues to show high recurrence rates, highlighting the need for new therapies that can effectively target that quality and lower the recurrence rate. The newer discussion of combination therapy presents a more hopeful approach, as it targets multiple tumor pathways simultaneously. As this method also utilizes smaller doses of drugs, it also minimizes drug toxicity, allowing for prolonged treatments for patients. However, more research and clinical trials are needed to discover the more optimal and effective limits of combination therapy, combining the effects of multiple different therapeutic approaches.

Conclusion

Ongoing research into the hypoxic microenvironment of GBM shows significant promise for improving treatment outcomes and reducing resistance to existing therapies. In further understanding how hypoxia influences tumor behavior can lead to identifying optimal immunotherapy combinations that can treat GBMs. By focusing on the unique characteristics of the hypoxic and immunosuppressive microenvironment, researchers can develop more targeted and individualized treatment strategies that address the specific challenges posed by GBM. Future studies should emphasize the significance of the hypoxic microenvironment and explore ways to reverse oxygen deficiency. Combining these approaches with existing treatments could significantly improve the prognosis for patients with GBMs.

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