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Review Article

Glioblastoma Multiforme: A Review

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Abstract

In recent years, many research groups have begun to utilize bioengineered *in vitro* models of cancer to study mechanisms of disease progression, test drug candidates, and develop platforms to advance personalized drug treatment options. Due to advances in cell and tissue engineering over the last few decades, there are now a myriad of tools that can be used to create such *in vitro* systems. In this review, we describe the considerations one must take when developing model systems that accurately mimic the *in vivo* tumor microenvironment (TME) and can be used to answer specific scientific questions. We will summarize the importance of cell sourcing in models with one or multiple cell types and outline the importance of choosing biomaterials that accurately mimic the native extracellular matrix (ECM) of the tumor or tissue that is being modeled. We then provide examples of how these two components can be used in concert in a variety of model form factors and conclude by discussing how biofabrication techniques such as bioprinting and organ-on-a-chip fabrication can be used to create highly reproducible complex *in vitro* models. Since this topic has a broad range of applications, we use the final section of the review to dive deeper into one type of cancer, glioblastoma, to illustrate how these components come together to further our knowledge of cancer biology and move us closer to developing novel drugs and systems that improve patient outcomes. Glioblastomas are universally fatal cancers and contain self-renewing glioblastoma stem cells (GSCs) that initiate tumors. Traditional anticancer drug development based on in vitro cultures tends to select targets with low therapeutic indices and fails to effectively represent the tumour microenvironment's impacts. Glioblastoma multiforme (GBM) is the most common and aggressive form of brain cancer, with treatment options often constrained due to inherent resistance of malignant cells to conventional therapy. We investigated the impact of triggering programmed cell death (PCD) by using BH3 mimetic drugs in human GBM cell lines. Glioblastoma multiforme (GBM) has been characterized by the high incidence, therapy tolerance and relapse. The molecular events controlling GBM resistant to chemotherapy temozolomide (TMZ) remain to be elusive. Here, we identified WNT signaling was amplified by TMZ and mediated drug response in GBM. We found O6-methylguanine DNA methyltransferase (MGMT) was redundant to WNT-mediated chemoresistance, which was highly associated with p53 mutation status. In GBM with p53 mutation, loss of function of p53 downregulated miR-34a expression, which represses transcription of WNT ligand 6 (WNT6) by directly binding to 3′ UTR of WNT6 mRNA, leading to activation of WNT signaling, and the eventual WNT-mediated chemoresistance to TMZ. Combined treatment of TMZ with WNT inhibitor or miR34a mimic induced drug sensitivity of p53-mutant GBM cells and extended survival in xenograft mice in vivo. Our findings provide insight into understanding the molecular mechanism of GBM chemoresistance to TMZ and facilitating to develop novel treatment strategy to combat p53-mutant GBM by targeting miR-34a/WNT6 axis. Advantages and drawbacks of dexamethasone in glioblastoma multiforme: Dexamethasone has been used for many years to treat brain edema and inflammation caused by GBM.Several investigations have shown that dexamethasone also exerts antitumoral effects against GBM.Unfortunately, steroids are associated with various undesirable side effects. Herein, we review pre-clinical and clinical applications of Dexamethasone in GBM. The most widespread, malignant, and deadliest type of glial tumor is glioblastoma multiforme (GBM). Despite radiation, chemotherapy, and radical surgery, the median survival of afflicted individuals is about 12 months. Unfortunately, existing therapeutic interventions are abysmal. Dexamethasone (Dex), a synthetic glucocorticoid, has been used for many years to treat brain edema and inflammation caused by GBM. Several investigations have recently shown that Dex also exerts antitumoral effects against GBM. On the other hand, more recent disputed findings have questioned the long-held dogma of Dex treatment for GBM. Unfortunately, steroids are associated with various undesirable side effects, including

severe immunosuppression and metabolic changes like hyperglycemia, which may impair the survival of GBM patients. Current ideas and concerns about Dex's effects on GBM cerebral edema, cell proliferation, migration, and its clinical outcomes were investigated in this study. Glioblastoma multiforme (GBM) is one of the most common, most formidable, and deadliest malignant types of primary astrocytoma with a poor prognosis. At present, the standard of care includes surgical tumor resection, followed by radiation therapy concomitant with chemotherapy and temozolomide. New developments and significant advances in the treatment of GBM have been achieved in recent decades. However, despite the advances, recurrence is often inevitable, and the survival of patients remains low. Various factors contribute to the difficulty in identifying an effective therapeutic option, among which are tumor complexity, the presence of the blood–brain barrier (BBB), and the presence of GBM cancer stem cells, prompting the need for improving existing treatment approaches and investigating new treatment alternatives for ameliorating the treatment strategies of GBM. In this review, we outline some of the most recent literature on the various available treatment options such as surgery, radiotherapy, cytotoxic chemotherapy, gene therapy, immunotherapy, phototherapy, nanotherapy, targeted therapy and tumor treating fields in the treatment of GBM, and we list some of the potential future directions of GBM. The reviewed studies confirm that GBM is a sophisticated disease with several challenges for scientists to address. Hence, more studies and a multimodal therapeutic approach are crucial to yield an effective cure and prolong the survival of GBM patients.

Keywords: Glioblastoma multiforme, chemotherapy, radiotherapy, immunotherapy, cancer therapy, Gene therapy. Glioblastoma remains a challenging disease to treat, despite well-established standard-of- care treatments, with a median survival consistently of less than 2 years. In this review, we delineate the unique disease-specific challenges for immunotherapies, both brain-related and non-brain-related, which will need to be adequately overcome for the development of effective treatments. We also review current immunotherapy treatments, with a focus on clinical applications, and propose future directions for the field of GBM immunotherapy.

Risk Factors causing Glioblastoma

It often occurs in people with rare genetic conditions - Turcot syndrome, neurofibromatosis type 1 and Li Fraumeni syndrome. Certain causes as per GBM patients and physicians are as follows:-

1. Severe and Chronic Stress
2. Hereditary
3. Tension
4. Severe frequent headaches
5. Exposure to Heat
6. Exposure to Sun
7. Confusion
8. Age (mostly occurs in geriatric population)

Symptoms of GBM:-

1. Seizures
2. Fits
3. Headache
4. Blurred vision
5. Uprolling of eyeballs
6. Tongue twisting
7. Body hypotonia (decreased muscle tone)
8. Loss of appetite.
9. Changes in mood and personality.
10. Changes in ability to think and learn.
11. Speech difficulty of gradual onset.
12. Vomitting

Advantages and Limitations of dexamethasone in glioblastoma multiforme are Dexamethasone has been used for several years to treat brain edema and inflammation caused by GBM. Several investigations have shown that dexamethasone additionally exerts ntitumoral effects against GBM. Unfortunately, steroids are related to numerous undesirable side effects.

Causes of Glioblastoma

Glioblastoma (GBM), the most common primary adult tumor, remains incurable. Despite well-established standard-of-care therapies consisting of maximal safe tumor resec- tion, concurrent chemotherapy, and radiation followed by additional chemotherapy, the median survival remains consistently less than 2 years. Paradoxically, although spread outside the central nervous system (CNS) is rare, even with extensive surgical resection, the infiltrative nature of this disease makes it almost inevitable for recurrence. This characteristic of GBM makes immunotherapy a logical consideration, wherein activated immune cells can target even distant infiltrating and isolated tumor cells.

GBM microenvironment is a complex interaction of tumor and host cells with equally complicated cellular and humoral interactions. GBM stem cells (GSCs), also referred to as glioma-initiating cells (GICs), are a heterogeneous population of cells which are multipotent, undifferentiated, have the capacity for self-renewal, and are highly tumorigenic. Although there is increasing recognition that neuronal–glioma interactions are an important aspect of tumor biology and cancer growth, the impacts of these interactions on tumor progression and microenvironment are just now being investigated.

The increasingly recognized complexity of the glioma microenvironment with the impact of neuronal activity as a regulator of glioma progression.

GBM remains one of the most treatment-resistant cancers to both conventional therapies, such as radiation and chemotherapy, and immunotherapies that have revolutionized treatments of other cancers. The heterogeneity of this disease between patients, the

immunosuppressive tumor microenvironment, and the BBB present unique challenges for achieving durable therapeutic responses. The use of immunotherapy to treat GBM has shown significant promise in many preclinical studies.

GBM poses a significant treatment challenge, and we will need a continually deeper understanding of basic immunology, along with autoimmune diseases, such as inflammatory CNS conditions, e.g., multiple sclerosis, and chronic viral infections to better understand immune mechanisms within the brain. As our understanding of the complex microenvironment and new approaches for modulating immune function emerge, rationally designed combinations of immune therapies will hopefully lead to effective therapies that improve patient outcomes by providing long-lasting disease control.

Widely recognized risk factors associated with GBM occurrence are exposure to high dose ionizing radiation and certain genetic syndromes, including neurofibromatosis type 1 and Li-Fraumeni syndrome. The occurrence of GBM is higher in males and among individuals 50 years of age and older.

GBM is characterized by rapid cell proliferation and extensive invasion of tumor cells into the surrounding brain, making complete removal of the tumor impossible. These features lead to a high recurrence rate, even with the current treatment regimen of maximum safe surgical removal, radiation therapy and temozolomide chemotherapy. Intratumoral molecular heterogeneity, presence of the blood–brain barrier, and tumor immune evasion via local immunosuppression limits the success of existing therapies. Numerous drug therapies directed against GBM have shown promising results in in vitro assays, but all have had limited success in vivo. This is due in part to the diffuse, heterogeneous nature of the tumor, and the blood–brain barrier that limits the ability of many drugs to enter the brain parenchyma. Understanding the critical factors that restrict drug delivery to the brain is necessary to develop platforms for the enhanced delivery of effective drugs.

Gliomas account for almost 30% of primary brain tumors and 80% of all malignant ones. Based on their histo- pathological features, gliomas are traditionally classi- fied by the World Health Organization (WHO) as grade I and II (low-grade gliomas), grade III (anaplastic) and IV (glioblastoma) [1], which indicate different degrees of malignancy. In recent years, with the development of genomic, transcriptomic and epigenetic profiling, sub- stantial advances have been achieved in new concepts of classifying and treating gliomas, which will complement the morphology-alone-based classification. The classification of molecular subtypes within the glioma facilitates molecular diagnosis in a timely manner to offer opportunities to select the proper treatment modality according to the demand of clinical practice. Glioblastoma (GBM) is the most common and aggressive type of primary brain tumors, which comprises up to 50% of all gliomas. Despite progress made in the cur- rent standard of care including surgery, radiotherapy, and pharmacotherapy (typically chemotherapy with concomitant temozolomide (TMZ)), the outcome for patients remains almost universally lethal, with a median overall survival (OS) ranging from 14.6 to 20.5 months. The prognosis is much worse in elderly patients, who have an average survival from diagnosis of less than 8.5 months.

The most common high-grade primary malignant tumour, glioblastoma (GBM), seems to have an extremely dreadful prognosis. Novel treatment strategies for GBM are considered essential, given the dismal prognostic with currently approved treatments. Using improved genetic or epigenetic profiling of glioblastoma, and the brain microenvironment and immune system interactions, centuries of investment in basic science of gliomas is rapidly translated into innovative clinical trials. Immunotherapy, such as immune checkpoint blockade, chimeric antigen receptor T (CAR T) cell therapy, oncolytic virotherapy, and vaccine therapy, have offered new hope for improving GBM outcomes as a result of these encouraging findings; ongoing studies are using combinatorial therapies with the purpose of decreasing adverse side effects and augmenting antitumor immune responses. Techniques to break through the blood-brain barrier are also being researched.

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