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■ REVIEW ARTICLE

Isocitrate Dehydrogenase Defects In Gliomas: PATH For Potential Therapeutics

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ABSTRACT: Gliomas are a common type of brain tumor that begins in the glial cells of the brain or spinal cord. IDH1 and IDH2 genes, encoding for the Isocitrate Dehydrogenase (IDH), are frequently mutated in gliomas, which leads to the conversion of αKetoglutarate (α-KG) to 2-Hydroxyglutarate (2-HG). This leads to several epigenetic changes in the genome, further leading to the activation of tumor cells in the brain. The mutation in the IDH1 gene also suppresses the immune system, offering new potential that can lead to the development of drugs and therapies that particularly target and strengthen the immune system. Due to the potential successes of new immunotherapy treatments, gliomas can be treated more effectively. Despite these successes in immunotherapy treatments for gliomas, further research needs to be conducted on the types of mechanisms by which drugs and immunotherapeutic treatments treat different gliomas. Through this paper, I hope to discuss the effects of IDH1 mutation in glioma cells and the potential therapies to treat gliomas. I further wish to discuss the potential benefits of combination therapeutics over monotherapy.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Glioma; IDH1; Combination Therapeutics.

■ Introduction

Gliomas are the most prevalent type of primary malignant brain tumor originating in the glial cells located in the central and peripheral nervous system.[1] Glial cells support the neurons by controlling synaptic signaling and ensuring homeostasis inside the neuron's environment.[1] In gliomas, however, glial cells become cancerous and grow rapidly.[2] A depiction of normal brain and cancer-infiltrated brain tissue is shown in Figure 1. The WHO classifies gliomas into 4 categories from Grade I to Grade IV, with Grades I and II considered low-grade and Grades III and IV considered high-grade.[3] Astrocytomas, typically low-grade and originate in children, are the most common types of gliomas and originate in the astrocytes of the glial cells.[3] Glioblastoma Multiforme (GBM), grade IV astrocytomas in adults, are highly infiltrative and rapidly spread to other body parts.[4] Other types of gliomas include oligodendrogliomas, which originate from cells that produce myelin (oligodendrocytes), and Ependymomas, which originate from ventricular linings of ependymal cells and are common in pediatric patients.[4]

Gliomas, especially GBMs, are challenging to treat due to the fast-spreading nature of the tumor and the potential effect of the tumor on the microenvironment of the immune system.[5] In the United States, there are approximately six cases for every 100,000 people diagnosed with glioma each year, with an average life expectancy of just 15 months after standard treatments such as radiation, chemotherapy, and surgery.[4,6] However, the incidence and rate of gliomas can differ based on gender and age. For instance, GBMs, which are the most lethal form of primary malignant tumor, are more prevalent in ages between 75 and 84, with survival of approximately only 9 months after standard treatments.[7] Research also suggests that primary malignant gliomas are more common in males than in females, with the greatest difference of 30% between males and females over the age of 45.[8] Due to low prognosis and the highly variable nature of gliomas, it is very difficult to find definitive and standardized forms of treatments for gliomas. Although research has been done to treat various types of gliomas, much of the research is focused on inhibiting the defective enzymes or mutated genes involved in tumor progression, which is ineffective in treating high-grade gliomas such as GBMs. Comprehensive knowledge about the enzyme involved in tumor progression is required to target gliomagenesis effectively.

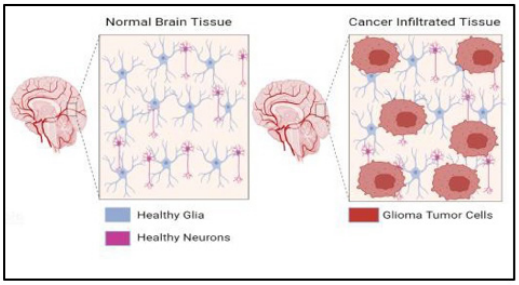

Figure 1: The image shows how normal brain tissue and brain tissue infiltrated by glioma cells are different in composition, which can affect the functioning of the brain and the entire body. They are created with BioRender.com.

Isocitrate Dehydrogenase (IDH) is an essential enzyme in the tricarboxylic acid cycle to convert isocitrate to alpha-ketoglutarate (α-KG).[9] Mutation in the Isocitrate Dehydrogenase 1 (IDH1) gene has been known to lead to the further conversion of α-KG to D-2-Hydroxyglutarate (D2-HG), a subtype

DOI: 10.36838/v6i7.8

of 2-HG which is considered an oncometabolite (Figure 2).10 D2-HG introduces hypermethylation phenotype through genome-wide epigenetic changes by inhibiting the α-KG-dependent dioxygenases, which would further lead to initiation of tumor formation in the brain.[11,12] Because IDH mutations typically occur during the very early stages of gliomas and are present in greater than 80% of grade II/III glioma cases, it is very important to learn about the effects of IDH mutations and the accumulation of D2-HG on glioma progression to find effective treatment options for gliomas.[13,14] Although several small molecule inhibitors in the form of drugs have been identified to target mutant IDH enzymes, the efficacy of such drugs is largely questioned in high-grade gliomas such as GBMs.[15,16] Therefore, more effective treatment interventions must be used to slow down or prevent glioma progression to increase the efficacy of treatments in all types of gliomas.

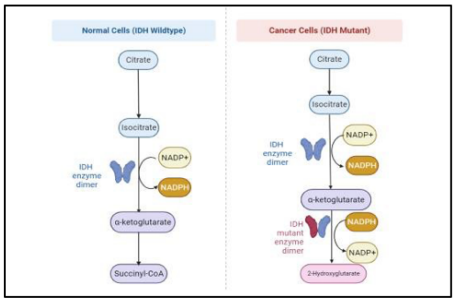

Figure 2: The flowchart compares normal cells with the wild-type IDH1 gene and glioma cells with the IDH1 gene. The IDH wildtype cells produce α-KG, ensuring normal functioning, whereas IDH mutant cells produce 2-HG, an oncometabolite that triggers glioma–created with BioRender.com.

Immunotherapy involves strengthening the immune system to induce an immune response that attacks unhealthy/foreign cells.[17,18] Recently, the production of D2-HG has been known to affect the microenvironments of immune cells, leading to a suppressed immune system due to the inability of T-cells to eliminate abnormal cells and inducing tumor progression.[13] Although many immunotherapeutic treatments directly targeting the tumor microenvironment (TME), including T-cell therapy and peptide vaccines, are currently being tested, the majority of trials involving monotherapies proved to be ineffective in stopping gliomagenesis; however, when these techniques are combined with other forms of treatments, the efficacy of glioma therapeutics is greatly increased.[19-22] Therefore, through this paper, I plan to discuss forms of combination therapeutics that can be clinically tested and effectively used to treat all gliomas, including GBMs. In this review paper, I first explain the effects of IDH1 mutation on glioma cells by explaining how the altered immune TME negatively affects the anti-tumor immune response. Through this knowledge, I will discuss how combining treatments such as immune checkpoint inhibitors, vaccines, chemoradiotherapy, and CAR T-cell therapy can prevent gliomagenesis. This research will serve as an important guide for extensive research in the modern fields of neurological, immunological, and oncological medicine, which can lead to advancements in treatments of severe types of gliomas.

Section 1: Mutations in Gliomas:

The IDH enzyme, encoded by the IDH1 gene, is responsible for the decarboxylation of isocitrate to α -KG.[23] In gliomas, there is a frequent point mutation (substitution) in codon 132 of the IDH1 gene, which results in the substitution of adenine (A) in place of guanine (G), changing the resulting amino acid sequence from arginine (Arg) to histidine (His).[14,23] The mutant IDH1 gene renders the IDH enzyme defective as it alters its active site residues, changing its shape and preventing it from binding to isocitrate.[24] Instead, the defective IDH enzyme will have an increased affinity for α -KG, leading to the formation of D2-HG from α-KG, known to initiate tumorigenesis due to its genome-wide hypermethylation.[11] However, along with IDH1, Tumor Protein 53 (TP53), Epidermal Growth Factor Receptor (EGFR), and Neurofibromin 1 (NF1) are also frequently mutated in gliomas and contribute to gliomagenesis.[23,25] Despite this, TP53, EGFR, and NF1 do not serve as important markers for the initiators of gliomas and serve little to no prognostic value despite several studies demonstrating their importance in gliomagenesis.[26] Thus, IDH1 mutation is an important marker for detecting gliomas. It is frequently mutated early on in glioma progression and predicts the occurrence of gliomas better than the other genes.[10,26] Nonetheless, before diving deeper into the therapeutic aspects that the IDH1 gene offers, it is important to understand the mechanisms by which IDH1 mutations lead to epigenetic modifications and affect the immune microenvironment of gliomas.

Section 2: Epigenetic Modifications in Gliomas:

DNA and Histone Methylation are important processes that control transcriptional and gene regulation.[27,28] DNA Methylation involves adding a methyl group to the cytosines that precede the guanines in the DNA structure, silencing the gene and preventing RNA Polymerase from transcribing DNA.[26,29,30] On the other hand, histone modifications involve adding methyl groups to the histone tails, leading to either the activation or inhibition of a gene.[28,31-33] However, in gliomas, the excessive production of D2-HG due to the IDH1 mutation has been shown to lead to epigenetic dysregulation through genome-wide hypermethylation phenotype, triggering the initiation of gliomagenesis.[11,34] Further research shows that D2-HG is a competitive inhibitor of α-KG-dependent dioxygenases; D2-HG prevents α-KG from binding to the active site of the dioxygenases, preventing the enzymes from regulating gene expression.[13,35,36] The similar structures of α-KG and D2-HG make this inhibition possible (Figure 3).[13]

DOI: 10.36838/v6i7.8

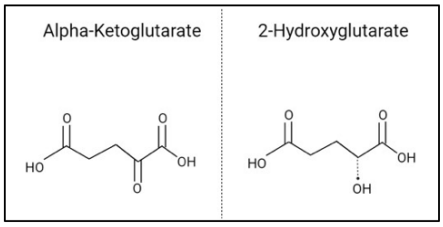

Figure 3: This image depicts the structural similarity between α-KG and 2-HG. Both the compounds essentially have equivalent structures, but they differ by only one different functional group: α-KG has a carbonyl group in place of a hydroxyl group that 2-HG has. This allows 2-HG to directly compete with α- KG for the active site of α-KG-dependent dioxygenases, serving as an oncometabolite. They are created with BioRender.com.

Ten-eleven translocation (TET) Hydroxylases and Lysine-Specific Demethylases (KDMs) are two groups of dioxygenases that are inhibited by D2-HG and cannot perform their function of demethylating the DNA and demethylating the histone tails respectively (Figure 4).[11,37,38] This dysregulation of epigenetic modification due to the excessive production of D2-HG leads to genome-wide hypermethylation and initiation of gliomagenesis. Furthermore, this hypermethylation phenotype also suppresses the immune TME and prevents immune cells from eliminating tumor cells.[39] Thus, a comprehensive overview of the immune TME is required to understand the mechanisms of gliomas.

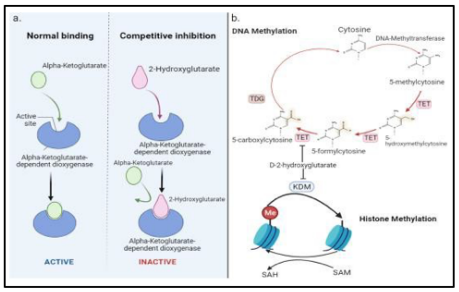

Figure 4: Schematic representation of competitive inhibition of α-KG-dependent dioxygenase by D2-HG that leads to hypermethylation phenotype. (a) The illustration depicts how competitive inhibition of α-KGdependent dioxygenase occurs due to the presence of 2-HG. (b) Schematic depicts the inhibition of TET Hydroxylases and KDMs by D2-HG on the regulation of genome-wide methylation. It was created with BioRender.com.

Section 3: Tumor-associated Microenvironment:

Tumor microenvironment (TME) refers to the complex ecosystem in which malignant cells interact with other groups of non-malignant (or stromal cells).[40] The immune cells in the TME communicate with the microenvironment through various junctions and other cellular components, including glycoproteins and cytokines.[41-43] The brain-blood barrier (BBB) is an essential part of the central nervous system (CNS) and TME that limits the passage of immune cells and other materials essential for the survival and functioning of the brain.[40] Tight junctions are an important part of the Blood Brain Barrier (BBB) that enables the BBB to limit the passage of immune cells and other materials essential into the brain for the survival and functioning of the CNS.[44] Due to the immunosuppressive environment created by D2-HG production in gliomas, however, these tight junctions cannot function normally, and the BBB will allow a lot more substances to pass through it, including the infiltration of immune cells into tumors, which is known to initiate gliomagenesis.[45-49] Although the BBB is disrupted in gliomas, it still maintains its function peritumorally, which makes the passage of therapeutics across the BBB very difficult, allowing the infiltrative components of gliomas to be protected by therapeutics and drugs.[15,40,50] Due to the extremely heterogeneous and selective BBB, the efficacy of glioma treatments is extremely low.[49] Despite many studies finding new techniques to target BBB, new and better ways must be developed to ensure that the BBB is penetrable and allows the passage of therapeutics.[40]

The immunosuppressive TME in gliomas occurs due to the dysfunction of several components of the TME, including Immune-Cell Checkpoints, Major Histocompatibility Complex (MHC), Tumor-Associated Macrophages (TAMs), Natural Killer Cells (NK), Dendritic Cells (DCs), and other immunosuppressive factors.[51-54] The normal roles and the roles in gliomagenesis of these components are summarized in Table 1. The combined dysfunction of these components prevents T-cell activation, leading to tumor formation and gliomagenesis (Figure 5). All of these components, along with their role in immunosuppression, are described below.

Table 1: This table shows the normal functions of different components of the immune TME along with their roles in gliomas.

IMMUNE COMPONENTS	NORMAL FUNCTION	FUNCTION IN GLIOMAS
PD-1/PD-L1	Regulation of Immune Homeostasis	Inhibit immune response and reduce T-cell activity
CTLA-4	Regulation of Immune Homeostasis	Inhibit immune response and lead to T-cell arrest
MHC	Present tumor antigens to T-cells	Cannot present tumor antigens to T-cells
TAMs	M1 Phenotype directly mediates the elimination of T-cells	M2 Phenotype causes an immunosuppressive environment
NK Cells	Directly eliminate tumor cells without requiring antigen presentation	Activate T-regs to inhibit T-cell proliferation
DCs	Present antigens to T-cells	Recruit T-regs to prevent T-cell proliferation
Immunosuppressive Factors (TGF-β & IL-10)	Regulation of Immune Homeostasis	Too much immune inhibition that prevents elimination of tumor cells

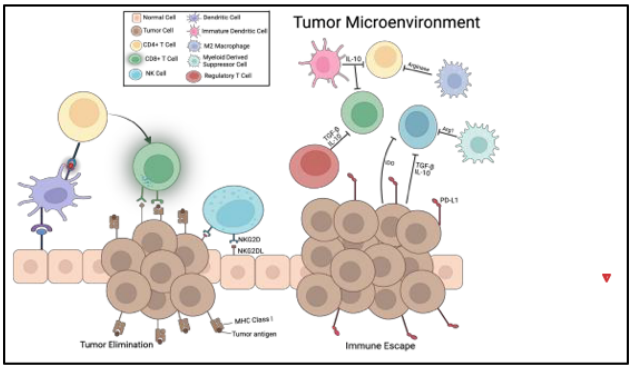

Figure 5: This schematic depicts the difference in the interaction of the TME components when the tumor cannot escape an immune response as opposed to when it can escape an immune response. When tumor cells cannot escape the immune response, DCs present antigens to T-cells to initiate an immune response to eliminate tumor cells. However, when tumor cells escape the immune response, all the TME components suppress T-cells' ability to initiate an immune response, leading to tumorigenesis. They are created using BioRender.com.

Immune-cell Checkpoints:

Immune-cell checkpoints are a series of pathways that regulate the immune response and prevent it from being so powerful that it destroys healthy body cells.[55] However, in gliomas, overexpression of these checkpoints creates an immunosuppressive environment. It prevents the immune system from attacking cancer cells by stopping T-cell proliferation and leading to T-cell death.[53] Two checkpoints (PD-1/PD-L1 and CTLA-4) and their role in tumorigenesis are included below.

Programmed cell death 1 / Programmed cell death ligand 1 (PD-1/PD-L1):

Programmed cell death 1 (PD-1), a receptor present on the surface of T-cells, NK cells, and TAMs, binds to its ligand, PD-L1, which activates a pathway that inhibits T-cell proliferation, allowing tumor cells to escape immune response and grow uncontrollably.[56,57] This further leads to the formation and spread of tumors in tissues surrounding the affected body part.[57] Furthermore, this pathway is greatly activated by certain immunosuppressive factors that contribute to an immunosuppressive TME.[53,58] Because this pathway plays an important role in initiating tumorigenesis by allowing tumor cells to escape immune response, this pathway serves as a great immunotherapeutic target for cancer treatment.

Cytotoxic T-Lymphocyte-associated protein 4 (CTLA-4):

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another receptor on T-cells in the immune system.[59] Similar to PD-1/PD-L1, CTLA-4 also activates a pathway that causes T-cell arrest, which prevents T-cells from eliminating harmful tumor cells, initiating tumor formation due to the suppressed immune TME.[60] Targeting CTLA-4 with an anti-CTLA-4 antibody has been known as an effective treatment for preventing tumorigenesis through the activation of T-cell proliferation to eliminate tumor cells.[61,62] More evidence is needed to accept anti-CTLA-4 as an effective treatment.

Major Histocompatibility Complex (MHC):

MHC is a group of genes that code for proteins on the cells' surface and aid the immune system in recognizing foreign substances by presenting antigens to Cytotoxic T-lymphocytes (CTLs).[63] MHC binds to internal antigenic peptides and transports them onto the cell surface so that those antigens can be recognized by CTLs, which eliminate tumor cells.[64] However, in gliomas, certain cytokines, such as Transforming Growth Factor-ß (TGF-ß) and Interleukin-10 (IL-10), are released in the TME, which downregulate the activity of MHC by preventing the process of antigen presentation from occurring through the activation of PD-1/PD-L1 checkpoint, leading to T-cell arrest.[53,54,65] The loss of function of MHC is directly related to more severe gliomas as the ability to present antigens onto T-cells is lost, leading to an immunosuppressive TME and a worse prognosis.[66] Therefore, the MHC must be effectively targeted to elicit an appropriate immune response.

Immune Cells

Tumor-associated Macrophages (TAMs)

TAMs are an essential part of the immune system and comprise about 30% of the tumor mass in malignant gliomas.[67] TAMs are divided into two subtypes: M1 and M2.[68] M1 phenotype plays an important role in inducing anti-tumor resistance and fighting pathogens.[69] However, the problem occurs when M1 changes to M2 phenotype, leading to the suppression of the immune system.[70,71]

In gliomas, the M2 phenotype is caused by the production of D2-HG, which causes the release of immunosuppressive factors such as IL-10 and TGF-β in TAMs. This leads to tumor cells' resistance to potential vaccines and therapies by evading immune defense.[72-75] Essentially, when TAMs are in the M2 phenotype, T-cells cannot recognize and eliminate tumor cells, leading to tumor progression.[75,76] Therefore, targeting TAM as part of potential therapeutics for treating gliomas is essential.

Natural Killer (NK) Cells:

NK cells are white blood cells that eradicate or lyses cells infected by viruses without requiring antigen presentation to activate them.[77,78] In gliomas, however, due to the presence of the cytokine TGF-β, there aren't enough NK cells to induce lysis of tumor cells as the activating receptor, Lectin-like receptor K1 (NKG2D), of NK Cells is downregulated.[79,80] This would contribute to an immunosuppressive TME, meaning that the tumor cells could escape an immune response, preventing the immune system from targeting the cancer cells.[81]

Dendritic Cells (DCs):

DCs are antigen-presenting cells (APCs) responsible for repairing the TME by engulfing the antigens and presenting them to T-cells or B-cells, leading to an immune response and destruction of foreign and tumor cells.[82] However, during gliomas, due to certain chemokines such as TGF- β in the TME, instead of recruiting CTLs, DCs activate regulatory T-cells (Tregs), which are known to inhibit or stop T-cell proliferation.[83] Furthermore, the presence of IL-10, which the TAMs generate, inhibits the maturation of DCs and stimulates immature DCs to increase, which inhibits the presentation of antigens onto T-cells, leading to an even more immunosuppressive TME due to the production of even more TGF-β.[52,84] This immunosuppressive TME leads to gliomagenesis as the immune system, particularly the T-cells, cannot attack the dangerous tumor cells.

Section 4: Potential Therapeutics:

Many treatments have been researched and tested in clinical settings for IDH1 mutation in gliomas, including the elimination of D2-HG directly by inhibiting mutant IDH enzyme or the inhibition of DNMT to inactivate hypermethylated genes, stopping the spread of glioma cells.[85-87] However, these forms of treatments by themselves aren't an effective form of monotherapies due to the highly variable nature of gliomas; they must be combined with other treatments to obtain efficient results.[88] Currently, the standard form of treatment used in gliomas is surgical resection (or tissue removal) followed by a combination of radiation and chemotherapy (through intake of temozolomide) to target cancer cells directly.[89] However,

DOI: 10.36838/v6i7.8

ing high-grade gliomas, including GBMs, with a survival rate of about 15 months and a 2-year life expectancy of less than 30%.[6] Due to the low efficacy of this treatment, there have been recent advances in immunotherapy as a form of possible treatment.[90,91] Due to the immunosuppressive TME created in gliomas due to D2-HG production, CTLs are rendered ineffective, making the immune system an important therapeutic target.[77] Thus, immunotherapy must target the immune system directly, eliciting an immune response to attack and kill cancer cells.[18] Currently, many studies are testing the effect of immune checkpoint inhibitors and Chimeric Antigen Receptor (CAR) T-cell therapy to ensure T-cells can attack and eliminate glioma cells.[92-96] Moreover, different types of vaccines, such as DC, neoantigen, and peptide vaccines, have greatly improved the study of glioma treatment.[97-99] However, the efficacy of these immunotherapeutics differs from person to person. In fact, according to a study, less than 15% of the patients responded to the immune checkpoint inhibitors in various types of cancers.[100] Nevertheless, when these forms of immunotherapeutics are combined with other treatments, the efficacy of glioma therapeutics has greatly increased.[22,101] Combination therapeutics have given hope for treating high-grade gliomas like GBMs and are being extensively researched. The different immunotherapeutic treatments, such as immune-checkpoint inhibitors, vaccines, and CAR T-cell therapy, are described below, along with combination therapeutics for glioma treatments.

Immune-Checkpoint Inhibitors:

Inhibition of the immune checkpoints PD-1/PD-L1 and CTLA-4 using monoclonal antibodies allows the T-cells to remain activated and attack and degrade tumor cells (Figure 6). [102-104] However, in gliomas, the use of these inhibitors as monotherapies has failed in several clinical trials, including the phase III failure of clinical trials to treat GBM.[105] The main reason behind the failure of these immune checkpoint inhibitors is that the production of D2-HG in IDH1 mutation in gliomas serves to inhibit the PD-1/PD-L1 pathway due to the hypermethylation of genes in the genome.[106] Therefore, immune checkpoint inhibitors are not recommended as the sole therapy for gliomas since they would not affect T-cell activation; this type of therapy must be used along with other therapies to ensure a better clinical outcome.[107]

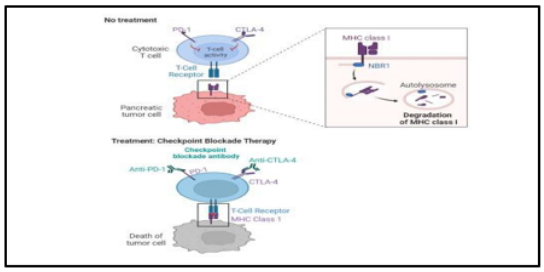

Figure 6: The schematic depicts the difference in T-cell activity when they were not treated with immune checkpoint inhibitors and when treated with the inhibitors. When no treatment of checkpoint blockade antibodies is used, the class 1 MHC is degraded, which prevents the presentation of tumor antigens to the T-cell receptor. However, when the immune checkpoint is inhibited, the functioning MHC class 1 presents tumor antigens to the T-cell receptor, leading to the destruction of tumor cells by Cytotoxic T-cells. They are created with BioRender.com.

Vaccines:

Vaccines targeting mutant IDH1 are becoming more prominent.[108] For instance, peptide vaccines are heavily being tested to mimic the epitope (site on the antigen to which an antibody binds) of an antigen to induce an immune response by activating CTLs to treat gliomas with defective IDH enzymes effectively.[97,98,109,110] Apart from peptide vaccines, neoantigen vaccines are also heavily being tested as a potential treatment for glioma; however, neoantigens are unique to tumor cells only, so the creation of neoantigen vaccines is specific to each patient.[77] Essentially, the neoantigen vaccines make tumor antigens available to be recognized by either DCs or macrophages. This allows the MHC to present those antigens to T-cell receptors, enabling CTLs to eliminate tumor cells and stop tumorigenesis.[77,111,112] Although neoantigen vaccines offer great therapeutic potential for IDH1 mutation in gliomas, research has shown that the efficacy of glioma therapeutics can greatly be increased by utilizing them in conjunction with other immunotherapeutic treatments like immune-checkpoint inhibitors.[94,99]

Chimeric Antigen Receptor (CAR) T-cell Therapy:

Recently, there have been advances in glioma treatment with the use of CAR T-cell therapy, which involves growing T-cells in large numbers and engineering them in a way that involves inserting the gene for a specific receptor (Chimeric Antigen Receptor), allowing the T-cells to bind to antigens on tumor cell and eliminate tumor cells.[113] Despite the recent increase in the CAR T-Cell Therapy treatment for gliomas, there are very limited implications for IDH1 mutations as most of the research involves focusing on Epidermal Growth Factor Receptor variant III (EGFRvIII) and human epidermal growth factor receptor II (HER2).[114,115] However, there are still some ongoing trials with CAR T-Cell Therapy that could help treat IDH mutant gliomas.[115] For instance, NKG2D, a receptor on NK Cells, is targeted by CAR T-Cell Therapy to activate NK Cells and trigger an immune response to stop gliomagenesis.[116] Due to the immunosuppressive TME created by D2-HG production in gliomas, the NKG2D receptor's efficacy in eliminating tumor cells decreases, contributing to gliomagenesis.[117] However, when the NKG2D are engineered into CAR T-cells, the efficacy for glioma therapeutics has greatly been increased with complete elimination of tumors.[118] Nevertheless, the target of NKG2D ligands via CAR T-cell therapy is still a relatively new idea. More clinical testing is needed to conclude whether it is an effective treatment for IDH1 mutation in gliomas.[115] Moreover, using CAR T-cell therapy with other treatments might be a better option than using it as a singular treatment.[119]

Combination Therapeutics:

Several different therapeutic treatments are known to treat gliomas. However, more treatments are less effective than monotherapies and must be combined with other treatments to ensure a better therapeutic outcome due to the highly heterogeneous nature of gliomas.[120] Immune checkpoint inhibitors have shown significant therapeutic potential for cancer treatments.[93] However, in IDH1 mutant gliomas, those checkpoint inhibitors are ineffective as a solo treatment

because the D2-HG-derived hypermethylation phenotype inhibits the immune checkpoints.[106,121,122] Thus, research has shown that the anti-PD-1 and antiCTLA-4 antibodies must be used along with mutant IDH1 inhibitors, radiation, and temozolomide intake to ensure an effective treatment.[123] In addition, the combination of CAR T-cell therapy and immune checkpoint inhibitors has been shown to increase gliomas' therapeutic potential by reducing Treg cells' inhibitory activity while also activating CTLs.[124,125] Furthermore, decitabine, a chemotherapeutic drug, is known to induce the expression of NKG2DLs and activate NK cells to attack and kill glioma cells.[126] Additionally, the combination of neoantigen vaccines and immune checkpoint inhibitors of PD-1/PD-L1, such as Nivolumab and Durvalumab, also offer better therapeutic potential than using neoantigen vaccines or immune checkpoint inhibitors as monotherapies.[127,128]

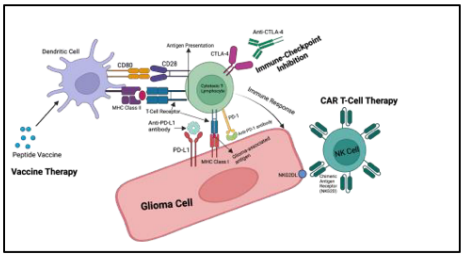

Figure 7: · This image depicts the mechanisms of three different combination therapeutics: Vaccine Therapy, immune checkpoint inhibitors, and CAR T-cell therapy. Furthermore, it illustrates the benefit of combination therapeutics in eliminating glioma cells over standard monotherapies. It was created with BioRender.com.

Discussion & Conclusion

There is currently a lot of research surrounding IDH1 mutation in gliomas, with many different therapeutics known to reduce the tumor's effects. However, the highly variable nature of gliomas due to genome-wide epigenetic changes caused by D2-HG production makes gliomas very difficult to treat. Specifically, the heterogeneity caused by the BBB, which protects the infiltrative parts of the TME while also preventing therapeutics from passing through it, contributes to the highly variable nature of gliomas. Furthermore, D2-HG is also known to suppress the immune system due to T-cell dysfunction, allowing tumor cells to escape immune response. Thus, the standard of care (chemoradiotherapy or surgery) for cancers or any immunotherapy used as monotherapies has proven to be ineffective in treating high-grade gliomas, including GBMs. Nevertheless, immunotherapy with the standard of care treatments or other immunotherapies has proven to be much more effective in directly targeting the mutant IDH1 gene and inducing the immune system. For instance, the use of immune checkpoint inhibitors along with CAR T-cell therapy and chemoradiotherapy has proven to significantly increase the efficacy of glioma therapeutics instead of utilizing these treatments as monotherapies.

Despite the great potential of combination therapeutics for IDH1 mutation in gliomas, more extensive research must be done to accept these treatments as the standard of care for gliomas. For example, using CAR T-Cell as a treatment for IDH1 mutant gliomas needs further research. Particularly, the mechanisms in which NKG2D can be targeted via CAR T-cell therapy to activate NK cells to induce an immune response must be further researched. Additionally, more research needs to be done on how the M2 phenotype of the TAMs can be targeted to induce an anti-tumor immune response since TAMs are the most abundant cell type in gliomas, and targeting them will ensure that the immune system is effectively induced to target glioma cells. The use of immune checkpoint inhibitors for IDH1 mutant gliomas seems counterintuitive since the immune checkpoint inhibitors are known to be inhibited due to the hypermethylation phenotype caused by D2-HG production, so more clarity and research would be instrumental in determining the efficacy of these checkpoint inhibitors in IDH1 mutant gliomas. The modern field of glioma therapeutics is filled with various treatments, including many immunotherapeutics; however, these treatments are not widely used as standard care. Many immunotherapeutic and combination treatments must be accepted as part of daily therapeutics to create better treatments. Research, experimentation, and acceptance of various treatments for gliomas are key to developing effective treatments with greater life expectancy. However, before acceptance, the side effects of these treatments must be carefully researched so that an effective treatment plan for a patient can be created depending on how his/her body responds to the treatments. These combination therapeutics offer a great prospect for IDH1 mutant gliomas; however, much must be learned to accept this new approach for glioma therapeutics.

Acknowledgments

I would like to thank my tutor and mentor, Dr Kif Liakath-Ali, for constantly helping me in this research journey and helping me draft my paper efficiently. I would also like to thank Adrian Bebenek for his useful suggestions on this paper. Furthermore, I would also like to thank the entire Indigo Research Team for their constant support and motivation during the difficult times of drafting this paper. Finally, I would like to thank BioRender for providing an effective tool for depicting schematic diagrams to help me understand the concepts better.

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DOI: 10.36838/v6i7.8