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REVIEW ARTICLE

Targeting Glioblastoma: The Current State of Different Therapeutic Approaches

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Abstract: ***Background*:** Glioma is the primary cancer of the central nervous system in adults. Among gliomas, glioblastoma is the most deadly and aggressive form, with an average life span of 1 to 2 years. Despite implementing the rigorous standard care involving maximal surgical removal followed by concomitant radiation and chemotherapy, the patient prognosis remains poor. Due to the infiltrative nature of glioblastoma, chemo- and radio-resistance behavior of these tumors and lack of potent chemotherapeutic drugs, treatment of glioblastoma is still a big challenge.

***Objective*:** The goal of the present review is to shed some light on the present state of novel strategies, including molecular therapies, immunotherapies, nanotechnology and combination therapies for patients with glioblastoma.

***Methods*:** Peer-reviewed literature was retrieved *via* Embase, Ovid, PubMed and Google Scholar till the year 2020.

***Conclusion*:** Insufficient effect of chemotherapies for glioblastoma is more likely because of different drug resistance mechanisms and intrinsically complex pathological characteristics. Therefore, more advancement in various therapeutic approaches such as antitumor immune response, targeting growth regulatory and drug resistance pathways, enhancing drug delivery and drug carrier systems are required in order to establish an effective treatment approach for patients with glioblastoma.

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1. INTRODUCTION

Cancer is the most common cause of death worldwide. Despite the development of new advances in various therapeutic approaches and expansion in current therapies, the number of patients with cancer is increasing every year [1]. Over the past years, the incidence of brain tumors has also increased significantly [2]. Among the brain tumors, glioblastoma is one of the most common and fatal type in adults [3]. In the United States, approximately 13,000 new cases of glioblastoma are diagnosed every year; almost 90% of these patients die within three years, and 50% of patients die within one year after diagnosis [4]. Conventionally, the primary therapeutic option for patients with glioblastoma includes maximum surgical removal followed by radiation therapy with concurrent chemotherapy with Temozolomide (TMZ) [5-7]. TMZ stands as the greatest breakthrough during the past decade and has improved the progression-free survival time and overall survival in patients with glioblastoma [7, 8]. However, despite these rigorous treatments, tumor relapse is almost inevitable due to aggressiveness of the tumor and resistance to chemo- and radiation therapy [9, 10]. To date, glioblastoma remains incurable, with only a median survival of 15 months [11]. Because the treatment options are not sufficient to provide long-term tumor control and survival benefit, more focused investigation involving the understanding of glioblastoma tumorigenesis, chemo- and radio-resistance is required for the establishment of new therapeutic approaches. For this purpose, several research groups have been studying different dimensions of therapeutic approaches, including targeted therapies, gene therapies, immunotherapies and hormonal therapies [12-20].

The identification and development of innovative therapeutic strategies for the treatment of patients with glioblastoma are imperious and are of critical concern. Due to the tumor resistance and its unresponsiveness to the standard therapies, there is an urgent need for the development of innova-

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tive strategies for patients with glioblastoma. Developing approaches for glioblastoma include various molecular therapies, immunotherapies as well as their combinatorial therapies along with standard adjuvant chemotherapies. The present review aims to shed light on the currently available novel therapeutics, including microRNA (miRNA) based therapies, immunotherapies, virus-based therapies, nano-therapies and combinational therapies targeting brain tumors, particularly glioblastoma.

2. ROLE OF CELLULAR SIGNALING

Pathway activation of different receptors of growth factors is assumed to be involved in the growth of glioblastomas. Therefore, identifying and targeting some common down-stream intermediates such as phosphatidylinositol 3-kinase (PI3K) /protein kinase B (Akt) and Ras /Mitogen-activated protein kinase (MAPK) pathways may open new therapeutic alternatives. Kesari *et al*., have shown that Farnesyltransferase is involved in the signal transduction of the Ras pathway. Lonafarnib and tipifarnib, inhibitors of Farnesyltransferase, have been assessed in clinical trials in glioma patients [21]. It has shown that LY294002, which is an inhibitor of PI3K, leads to the sensitization of a mutant glioma cell line to radiation therapy [22]. In a recent study, the importance of the CD133-AKT-Wnt signaling axis was demonstrated in glioma pathogenesis. The authors showed that CD133 functions as a cell surface receptor for the activation of the Wnt signaling pathway in an AKT-dependent manner in patient-derived CD133 positive glioblastoma cells. They examined the molecular differences, such as stemness, between a high and low amount of CD133 cells and their relations with AKT-Wnt signaling. This study presented a patient based scenario for targeted therapy and could help to improve personalized medicine by targeting the AKT signaling pathways [23]. Also, Tomar *et al*., showed that TMZ facilitated the activation of the Wnt/β-catenin pathway and PI3K/Akt pathway in U87 glioblastoma cells. TMZ augmented the expression of downstream targets of Wnt in a concentration- and time-dependent manner. Authors also showed that mammalian target of rapamycin (mTOR) pathway activation was enhanced when combined with TMZ in glioma cells [24]. Many studies have revealed the formation of autophagosomes by the activation of AMP-activated protein kinase (AMPK) in glioma cells as well as in other tumor cells [25, 26]. Also, the activation of mTOR was inhibited by the AMPK, therefore, this acted as an mTOR inhibitor [27]. It has been shown that mTOR displays a crucial role in autophagy, particularly in glioma cells [28, 29]. It is established that mTOR controls the autophagy in the cells through the activation of eukaryotic translation initiation factor 4E-binding protein (4E-BP1) [28]. Zhao *et al*., demonstrated that isogambogenic acid inhibited the phosphorylation of 4E-BP1 in U87 glioma cells [30]. Further, isogambogenic acid induced autophagy *via* activating AMPK expression and subsequently downregulating mTOR expression in glioma cells. Overall, their study showed that the AMPK-mTOR pathway plays an essential role in the suppression of glioma growth [30]. In addition to these signaling pathways, Kaya-Aksoy *et al*., studied the role of Harakiri (HRK) protein in glioblastoma pathogenesis. HRK protein is a BH3-only protein, which is one of the members of the apoptotic pathway B-cell lymphoma 2 (BCL-2) family. The authors showed that the overexpression of HRK protein caused apoptosis activation in glioblastoma cells. In addition, HRK interacts with tumor necrosis factor-related apoptosis inducing ligand (TRAIL). The external factors that contribute to the response of TRAIL also enhance the expression of HRK. In their *in-vivo* experiments, authors found that the enhanced expression of HRK inhibited tumor growth and improved the survival of mice with glioblastoma [31].

3. ROLE OF MICRORNAs

The majority of the human genome encodes non-coding RNA (ncRNA) and only a small portion (2-3%) of whole-genome encodes for specific genes [32]. The most widely studied ncRNAs are the miRNAs. The miRNAs are single-stranded ncRNA molecules of 21-25 nucleotides in length and are explicitly involved in gene-regulation at the post-transcriptional stage (Fig. **1**) [33]. They incorporate complex mechanisms of interference involving transcription activation, upregulation of proteins, interaction with RNA binding proteins, Toll-like receptors, and nuclear and mitochondrial transcripts [34]. The role of miRNAs has been extensively studied over the past decade in the pathogenesis of glioblastoma, although it has not been well established to date [13, 35]. Most of the studies are only limited to identify the significance of miRNAs as a prognostic factor and biomarker for assessing treatment response [36-38].

3.1. Selecting a Suitable MiRNA for Therapeutic Intervention

It is critically important to precisely define and understand the basis for selecting a miRNA for therapeutic applications. Wightman *et al*., explained in the early 1990s that the binding of lin-4 ncRNA to the 3' untranslated region (UTR) of lin-14 messenger RNA (mRNA) sequence led to repression of *LIN-14* gene, which described the ability of miRNAs to regulate the gene expression [39]. Over the years, promising results have surfaced, shedding light on the genetic make-up of the human genome. Also, the advancements in bioinformatics have speeded the process of deriving meaningful models to explain the genetic complexity of the human genome. In the last decade, several algorithms have been designed to assess the binding of miRNA to the specific mRNA sequence based on evolutionarily conserved sequence complementarity [40]. However, these algorithms may provide vague mRNA target sites; therefore researchers face challenges in selecting the suitable target for investigation, which can only be done by understanding the biological function of mRNAs according to their perspective.

3.2. MiRNA Mediated Gene Suppression

Earlier studies focused on understanding the role of miRNAs and exploiting them as prognostic and diagnostic markers. However, the discoveries during the past decade have reformed the idea for miRNAs in cancer research. Recently,

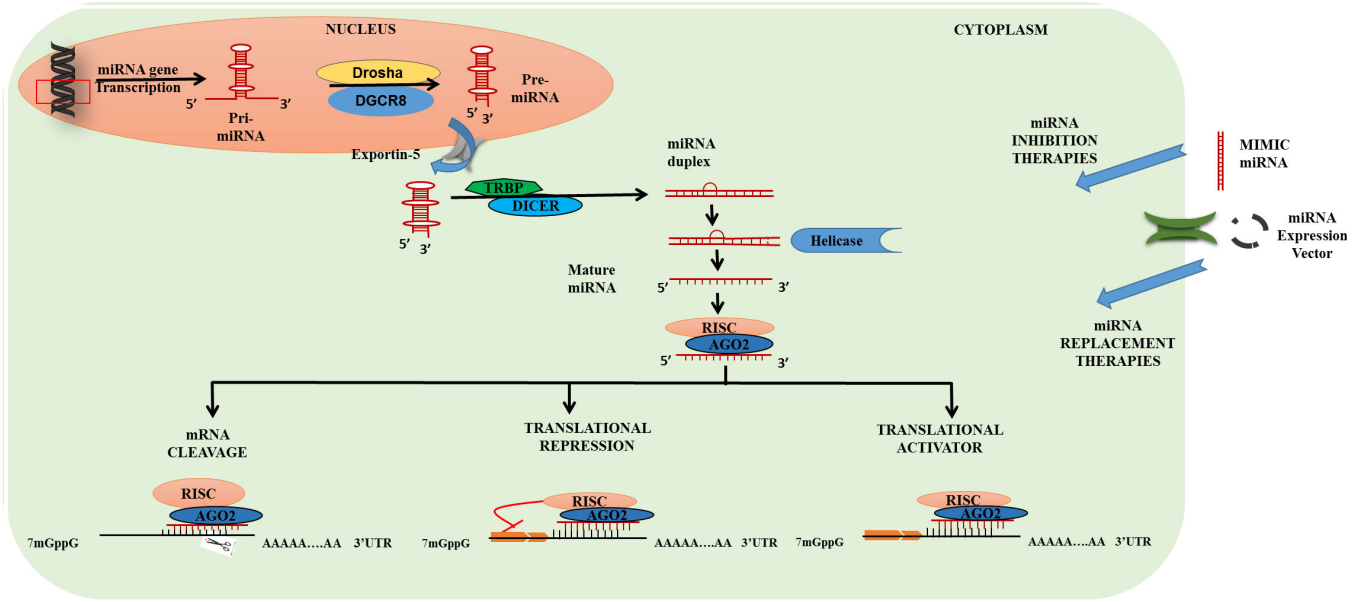

Fig. (1). miRNA biogenesis begins in the nucleus of the cell with cleavage of pri-miRNA to produce stemloop structure pre-miRNA by Drosha and DiGeorge Syndrome Critical Region 8 (DGCR8). Exportin5/Ran/GTP complex transports pre-miRNA to the cytoplasm. Dicer and TRBP (RNA-binding co-factor of Dicer) process the pre-miRNAs to miRNA duplex, which subsequently in the presence of helicase enzyme forms single-stranded mature miRNA. Later, mature miRNA complexes with RNA-induced silencing complex (RISC) in which Argonaute-2 (AGO-2) protein plays a central role. The seed region of the miRNAs recognizes and binds the 3'UTR of the target mRNAs and may affect the expression of genes through mRNA cleavage, translational repression, or translational activation. Current miRNA based inhibition therapies or replacement therapies that implement mimic miRNAs and miRNA expression vectors. MiRNAs inhibitory therapies involve suppressing the expression levels of oncogenic miRNAs on the contrary, replacement therapies involve the overexpression of tumor suppressor miRNAs through the expression of vector based delivery systems. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

few studies have attempted to explore the therapeutic aspect of miRNAs. Cellular metabolic re-programming is categorized as a hallmark for cancer development [41]. Cancer progression prompts an abnormal demand for cellular energy, which in turn potentiates the Adenosine triphosphate (ATP) and macromolecule production required for the proliferation of cancer cells [42]. The biological fuel needed for this cellular metabolism is the glycolytic intermediates, which make them crucial for tumor cell proliferation and on the other hand, they are crucial target for therapeutic intervention [43]. Cardoso *et al*., investigated the miRNA-based gene therapy in U87 and DBRTG cell lines targeting the aberrant glycolytic markers. They explained that miRNA-144 modulated the expression of enzymes involved in cellular bioenergetics pathways such as isocitrate dehydrogenases (IDHs), pyruvate dehydrogenase kinases (PDKs) and tumor protein 53 (TP-53) induced glycolysis and apoptosis (TIGAR), which in turn reduced the cell invasion and migration properties of glioma cells [44]. Brain cells are metabolically active, generating most of the energy from glucose metabolism [45]. Thus, brain tumor cells demonstrate higher dependence on glucose, which in turn, necessitates their metabolic adaptations [46]. Ogawa *et al*., selected the miRNA-451 as a therapeutic option based on their early findings. They explained the existence of a negative feedback loop between miRNA-451 and 5' AMP-activated protein kinase (AMPK), which is arbitrated by octamer-binding transcription factor 4 (OCT-4) transcription factor [47]. Later, miRNA-451 has been shown to reduce cellular migration of glioma cells both *in vitro* and *in vivo* [48]. Moreover, several other cellular signaling pathways have been shown to be deregulated in the carcinogenic process. Oncogenes are considered as potential targets in cancer therapies. *BCL-W* gene is categorized as an oncogene, which is associated with tumor progression and metastasis [49]. A study demonstrated the therapeutic effect of miR-340-5p in *BCL-W* oncogene overexpressing U87 and U251 glioblastoma cells. Initially, they observed that conditioned medium of *BCL-W* overexpressing glioblastoma cells presented enhanced tumorigenic phenotypes such as platelet-derived growth factor-A (PDGF-A) and cancer stem-like cell-related protein SRY-Box Transcription Factor 2 (SOX-2). Also, the transfection of these cells with miR-340-5p mimic downregulated the expression of *BCL-W* and *SOX-2,* thereby reducing invasion and cellular migration in glioblastoma cells [50]. In a similar study, high expression of fibronectin was shown to be associated with poor prognosis in patients with glioblastoma. It was reported that miRNA-1 expression is inversely related to fibronectin expression in orthotropic NOD.Cg-Prkdc^{scid} Il2rg$^{tm1Wjl/SzJ}$ (NSG) mouse models generated *via* MT330 cells. The study explained that animals implanted with miRNA-1 expressing cells demonstrated high survival with low infiltrative tumors

compared with animals implanted with control luciferase-expressing cells. The authors suggested tumor-suppressive function of miRNA-1 through inhibiting fibronectin in glioblastoma [51]. Further, Xu *et al*., suggested that integrin subunit alpha 9 (ITGA9) plays a prominent role in the proliferation and invasion of glioblastoma and can be a potential target for the targeted therapy. They explained that the overexpression of miRNA-148a led to reduced cell proliferation, invasion and migration in LN229 and U87 cells. Also this was shown to inhibit tumor growth in xenograft models [52].

Acquired drug resistance is one of the major factors for treatment failure in patients with glioblastoma. In a very recent study, chemosensitizing effects of miRNA-181a and carmustine were evaluated in the U373 glioblastoma cell line. The authors reported that miRNA-181a negatively regulated the proliferation of U373 cells *via* PI3K/AKT signaling. They found that miRNA-181a in combination with carmustine increased the apoptosis induction through modulating the expressions of B-cell lymphoma 2 (Bcl-2), caspase-9 and Sirtuin 1 (SIRT1) genes. Also, they reported aberration in cell cycle progression through increased G1 cell cycle arrest. Moreover, combining carmustine therapy with miRNA-181a decreased the clonogenic ability of U373 cells and inhibited cell migration by downregulation of matrix metallopeptidase 2 (MMP-2), BTB and CNC homology 1 (Bach1). Their results suggested that a combination of miRNA-181a and carmustine could be a potential therapy for glioblastoma [53]. Moreover, a recent study showed that miRNA-128a in combination with temozolomide treatment reduced the proliferation and migration of glioblastoma *in vitro* and *in vivo*. Further, their bioinformatics investigation revealed c-Met as the target gene for miR-128a. Their study concluded that c-Met, a receptor tyrosine kinase (RTK) protein, was a suitable target to enhance the chemosensitivity in U87 cells towards temozolomide [54].

Combinatorial approaches offer better chances for a positive outcome. Considering this, Bhaskaran *et al*., explored the concept of functional synergism to enhance the therapeutic efficacy of miRNA based therapy against glioblastoma. The authors hypothesized that incorporating more than one anti-tumor miRNA may provide an additive effect compared to a single miRNA treatment. They investigated the therapeutic effect of three antitumor miRNAs (miRNA-124, miRNA-128 and miRNA-137) in the glioblastoma mouse model system. Initially, the authors confirmed the low expression of miRNA-124, miRNA-128 and miRNA-137 and consequently confirmed higher expression levels of their target genes, *BMI1*, *EZH2* and *LSD1* oncogenes in both *in vitro* and *in vivo* studies. The authors later developed a lentiviral vector-based gene therapy to carry transgene encoding miRNA-124, miRNA-128 and miRNA-137 (cluster 3) [55]. Furthermore, to improve the antitumor efficacy of cluster 3, they also showed that extracellular vesicles could be a more promising option [55, 53]. It is of utmost importance to address that targets of these miRNA are derived using databases and *in-silico* approaches, which poses a risk of unknown non-specific binding of these miRNAs. Recapitulating the above-mentioned studies, miRNA-based therapeutics showed potential to be translated in clinical settings (Fig. **1**).

4. IMMUNOTHERAPIES

Over the last decades, the use of immunotherapy for various brain tumors has intensely grown and resulted in a better understanding of the interaction between the central nervous system (CNS) cancers and the immune system (Fig. **2**). Immunostimulatory gene therapy and immune checkpoint inhibitors might prove as a promising therapeutic approach for treating patients with glioblastoma. Among the various types of immunotherapies, T cell immunotherapy has recently become a promising therapy for brain tumors [56-58].

4.1. Immuno-regulators and Cytokines

Cytokine based therapies hold great potential for the treatment of cancer. They are a group of intracellular messengers that are capable of stimulating multiple cellular pathways. They are best known to stimulate and recruit immune cells in response to infection or abnormal cell proliferation [59, 60]. It is a well-known fact that there are several factors involved in the immunosuppression mechanism in glioblastoma. In their study, Quail and Joyce stated that several immune cells such as T cells, microglia and macrophages are recruited to the microenvironment of glioblastoma and showed immune-suppressive activities [60]. The immune response in glioblastoma can be inhibited by various immune--suppressive cytokines such as transforming growth factor β-1 (TGF-β-1) and interleukin (IL)-10 [61]. Also, it has been well established that glycoprotein A repetition predominant (GARP), which is a surface receptor present on activated regulatory T cells, plays a central role in the suppression of immune response in the tumor microenvironment. Further, it has been found that GARP has an inhibitory effect on T effector cells, and leads to tumor progression [62]. Another clinical study attempted to investigate the role of implemented peptide inhibitors to overcome the barrier of tumor-induced immune suppression. The authors targeted the activation receptor of CD200 checkpoint (CD200AR) *via* peptide inhibitor (CD200AR-L) in the macrophage cell line. The inhibitory peptide enhanced the antigen-specific immune response and also suppressed the expression of programmed death-1 (PD-1) and CD200 inhibitory receptors. Moreover, CD200AR-L also induced the dendritic cell maturation and cytokine/chemokine response [63]. Due to the immunomodulating effects of cytokines, researchers have recognized them as therapeutic targets for many types of tumor, including glioblastoma [64]. Most of the glioblastoma cells express T cell inhibitory ligands and secrete transforming growth factor β (TGF-β). TGF-β2 is a possible target for glioblastoma therapy because this cytokine is known to stimulate immunosuppression, tumor invasion and angiogenesis [65]. Hjelmeland *et al*., also reported that the growth of glioma is inhibited by using SB-431542, an inhibitor of the cytokine TGF-β2 in pre-clinical trials [65]. Also, TGF-β2 anti-sense oligonucleotides (AP12009) have been shown to exert anticancer activity without toxic side effects in early clinical trials [21]. In a similar study, Prasad *et al*., reported that

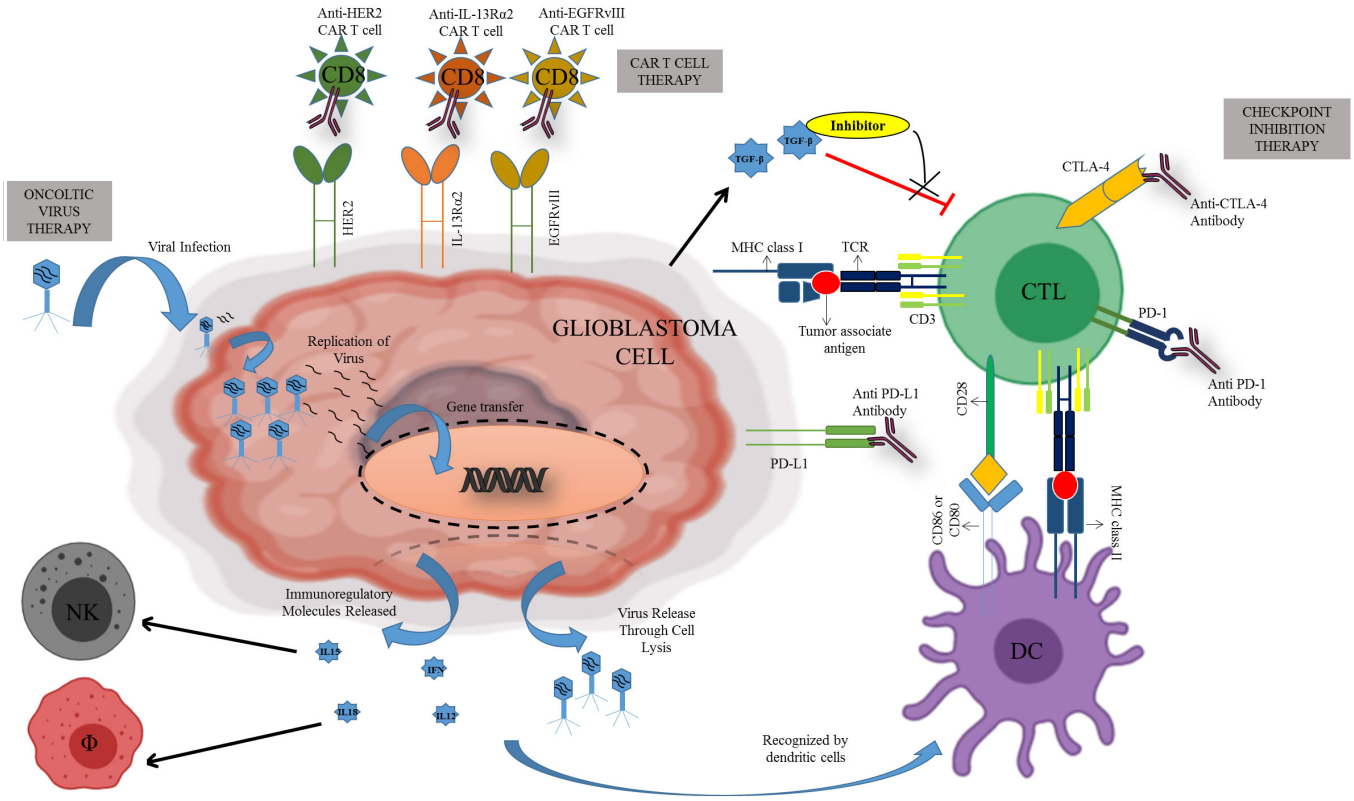

Fig. (2). Present immunotherapy strategies for glioblastoma: Oncolytic virus (OV) therapy, involves engineered designed to target tumor cells only. OV infection leads to tumor cell lysis and consequently triggers the immune response *via* dendritic cells (DC). In addition to that, some OV induce the release of immunoregulatory molecules like interleukin-15 (IL-15), interleukin-18 (IL-18), interferon (IFN) and interleukin-12 (IL-12) which can trigger immune system *via* DC, natural killer cells (NK) and macrophages (Φ). In adaptive immune response, DCs presents tumor antigens, virus particles or immunoregulatory molecules to Cytotoxic T lymphocytes (CTLs) *via* Major Histocompatibility Complex (MHC) class II and T cell receptor (TCR) on T cells or *via* surface receptors CD86 or CD80 on DC cells and CD28 on T cells. CTLs are responsible for destroying glioblastoma cells that are presenting antigens located on MHC class I molecules, through TCR and CD3 interactions. Immune checkpoint regulation involving Cytotoxic T lymphocyte ligandcytotoxic T lymphocyte protein (CTLA-4) complex and programmed cell death 1 ligand 1 (PD-L1) receptor which located on the cell surface of glioblastoma cells can interact with programmed cell death 1 receptor (PD-1) located on CTLs play a crucial role in the inhibition of activated lymphocytes. Also, transforming growth factor-beta (TGF-β) from tumor cells inhibit CTL function making it a therapeutic target. Checkpoint inhibition therapy is based on averting this ligand binding by specific monoclonal antibodies/inhibitors which bind to these receptors. Genetically engineered CD8+ T cells (CAR T), namely anti-HER2, anti- IL-13Ra2 and anti-EGFRvIII are designed to target respective tumor specific antigens HER2, IL-13Ra2 and EGFRvIII located on the cancer cell surfaces and eliciting tumor immune response. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

six of nine patients administered with IL-4 fused to Pseudomonas exotoxin (IL-4 cytotoxin) showed necrosis in tumors, without causing any damage to the neighboring tissues [64]. Furthermore, due to these promising results, phase II/III trials are in progress. Also, the expression of osteopontin (*OPN*) in glioblastoma and its role within the immune response have been studied [66]. *OPN* is a type of glycophosphoprotein, which also contains an arginine-glycine-aspartate (RGD) motif. To investigate its association with various grades of glioma, they silenced the *OPN* gene implementing siRNA and CRISPR/Cas9 methods in the mice models. It was suggested that glioblastoma with higher expression of *OPN* correlated with shorter survival. The knock-out *OPN* gene consequently resulted in a reduction of M2 macrophages in gliomas. Also, glioma cells became sensitive to $CD8^+$ T cell cytotoxicity. Therefore, the authors report that *OPN* is responsible for communication between the innate immune system and glioma cells and this feature could be used as a target for immune therapy approaches [66].

4.2. T Cell-based Therapies

Engineered T cell therapy has gained attention as a possible effective therapeutic approach for cancer. Previously, different malignancies such as sarcoma, leukemia, melanoma and lymphoma have been treated using engineered T cells in clinical trials [67-69]. However, the use of engineered T cells in treating solid cancers is still scarce. Presently, the engineered T cell-based therapy is being designed to target

solid tumors, including glioblastoma [17, 70]. In recent years, promising anticancer effect of chimeric antigen receptor (CAR)-T cell therapy for various cancers has been shown, and Food and Drug Administration (FDA) has also permitted two CAR-T products commercially [71-73]. CAR-T cell therapy is also being used for glioblastoma with promising results. The CAR-T cell therapy can enhance the survival of mice with glioma significantly by targeting the epidermal growth factor receptor variant III (EGFRvIII), which is expressed in approximately 30% of patients with glioblastoma [70]. Morgan *et al*., developed EGFRvIII targeted CAR-T cells using T cells from patients with glioblastoma and confirmed its therapeutic effect *in vitro* against glioma stem cell lines [74]. However, glioblastoma is characterized by high molecular heterogeneity within a single tumor [75]. This heterogeneous nature of glioblastoma limits the efficacy of the treatment *via* evading the targeted immune response. A recent study aimed to find an appropriate solution for tumor cells evading from CAR-T cells. In search for a novel target for CAR-T cells, Nehama *et al*., suggested B7-H3 as a potential novel target, which was found to be highly expressed in clinical specimens. They showed that B7-H3 targeted CAR-T cells demonstrated higher efficiency in targeting the tumor growth in both patient-derived neurospheres *in vitro* and murine xenograft models *in vivo* [76]. Treatment of *in vitro* CAR-T cells may not always be successful in patients with glioblastoma due to the presence of inhibitory ligand expressions like programmed death-ligand 1 (PD-L1) [77]. Therefore, Choi *et al*., worked on a universal EGFRvIII CAR-T cell, which can resist inhibition of PD-1 throughout three gene disruptions with the help of the CRISPR-Cas-9 system. These designed CAR-T cells showed increased activity in studies on glioblastoma models [77]. Furthermore, Brown *et al*., demonstrated that the routes of infusion of CAR-T cells to a patient with glioblastoma played a critical role in showing anti-tumor effect [17]. Their case study evaluated 2 delivery routes, including intraventricular infusion and infusion into the resected tumor cavity for interleukin-13 receptor alpha 2 (IL13Rα2) targeting CAR-T cells in a patient with recurrent glioblastoma. Although both routes (intraventricular and intracavitary) demonstrated a low toxicity pattern, but they showed different efficacy in suppressing tumor growth in distant sites. The intracavital delivery of IL13Rα2-CAR-T cells abrogated local tumor recurrence but the appearance of new distant lesions was observed. In contrast, the intraventricular delivery route demonstrated the suppression of local and distant tumor sites in all central nervous system [17].

4.3. Combinational Imunotherapies

Combinational therapies with the addition of immunotherapy to the chemotherapies are still under investigation. Several recent studies have explained different approaches to enhance the current immunotherapies against glioblastoma. Park *et al*., showed the combinational effect of anti-PD-1 and TMZ in an orthotopic murine glioblastoma model and they demonstrated a higher anti-tumor effect with combination treatment compared to treatment alone group [78]. One study investigated a neo-adjuvant therapy regime that could enhance the effect on anti-PD-1 immunotherapy [18]. They divided the patient group randomly as adjuvant anti-PD-1 immunotherapy and neo-adjuvant therapy. The patients in the neo-adjuvant group received 200 mg pembrolizumab before surgery, while patients in the adjuvant group did not receive any pembrolizumab before surgery. Post-surgery, both groups received adjuvant pembrolizumab with a dose of 200 mg every three weeks. They found that patients who received the neo-adjuvant treatment showed a decline in gene expressions in the tumor, which are related to cell cycle and increment in T cell population compared to the patients who received only adjuvant therapy. It was explained that neo-adjuvant inhibition of PD-1 monoclonal antibody induced an interferon response in the tumor microenvironment. Activated interferon response was mediated through activation of interferon-γ producing tumour-infiltrating lymphocytes and suppressing PD-1/PD-L1 [18]. Moreover, Wu *et al*., showed that the combination of anti-PD-1 and anti-CXCR4 exerted an additive effect and improved immune response in the tumor microenvironment, resulting in increased survival in murine models [79]. The importance of immunotherapies with checkpoint inhibitors has been well established in various types of cancer, yet their role is not well defined in patients with glioblastoma and further studies are warranted to explore their therapeutic benefits [80].

4.4. Personalized Immunotherapies

In the past several years, the identification of neo-antigens that can be implemented for developing novel immunotherapies has been under investigation. Keskin *et al*., described the effect of a personalized neo-antigen vaccine with multi-epitope in glioblastoma patients. The authors investigated the effect of the vaccine on patients with newly diagnosed glioblastoma with non-methylated methylguanine methyltransferase (MGMT) status in phase I/Ib study. The patients underwent vaccine treatment after surgical resection of the tumor, which was analyzed for neo-antigen identification. The patients, who received the neo-antigen vaccine but did not receive dexamethasone, were found to have an increased number of tumor-infiltrating T cells and a higher number of $CD8^+$ and $CD4^+$ T cells specific to the given neo-antigen. Furthermore, they showed that neo-antigen vaccine could travel to the tumor itself through peripheral blood circulation [81]. Hillman *et al*., showed that the vaccination of MVA-MUC1-IL2 cancer vaccine (TG4010) after irradiation with a dose of 8 Gy enhanced the survival of RenCa-MUC1 cell injected mice compared to irradiation or vaccine alone treatment [82]. Remy-Ziller *et al*., also reported in their preclinical studies that the combination of immune checkpoint inhibitors, anti-PD-1 or anti-PD-L1, with the TG4010 vaccine, led to the suppression of tumor growth compared to the vaccine alone in a mouse model with CT26-MUC1 tumors [83]. Similarly, dendritic cells (DCs) play a crucial role in anti-tumor immunity because of their capability of forming an immune response against the tumor. Therefore, DCs can be explored as a new approach for immunotherapy.

It was reported that patient-derived myeloid circulating dendritic cells (cDC2) with inhibited p38 mitogen-activated protein kinase pathway (p38i) showed promising results in preliminary studies. Also, they have proposed clinical trials to investigate this future next-generation DC vaccine for glioblastoma [12].

5. VIRUS MEDIATED ONCOSUPPRESSION AND IMMUNOMODULATION

The basis of virus-based therapies originated as an observation in leukemia patients showing no cancer growth after viral infection [84]. This clinical observation did not go unnoticed by the medical community and consequently, utilization of viruses in the treatment of cancer was initiated. Earlier investigations involved wild type viruses that lacked any efficacy or safety [85]. In the late 1990s, virus-based cancer therapies re-emerged as "Oncolytic Virus (OV)". OV is a virus that can infect and kill a cancer cell without posing any harm to normal cells [86]. Rapid development in recombinant molecular biology has enabled the development of more precise and targeted virus-mediated therapies (Fig. **2**). Recombinant viruses can be used to elicit the expression of antigen, which is specific to the tumor and can also genetically modify the cells. Moreover, these viruses can directly alter tumor microenvironment and tumor cells *via* up-regulating major histocompatibility complex, activation of inflammatory pathways and enhanced antigen expression [87]. Jiang *et al*., reported that in mice injected with B16 melanoma cells, co-delivery of the adenoviral vector carrying IL-12 gene and SB-505124 (TGF inhibitor) considerably reduced the tumor growth and enhanced the survival of the animals [88]. Moreover, it is also known that in a broad range of host cells, significant level of transgene expression can be obtained by recombinant virus-based genetic modification of cells [89]. In gene therapy, viral vectors can function as immunomodulating agents or exert tumor inhibition effects based on the genome modifications [90, 91]. In contrast to viral vaccines, which are mostly used to alter the immune cells, oncolytic viruses can directly infect tumor cells [92]. Genetically modified viruses or viruses, which are non-virulent in humans, have been used to enhance the specificity of viral oncolysis [90]. The incorporation of genes to boost the immune response against tumor cells is also possible through genetic modification of the viral genome [93]. Mathis *et al*., reported that oncolytic viruses require specific host cell surface receptors to bind and enter their target cells [94]. For instance, oncolytic viruses such as Herpes simplex virus type 2 (HSV-2) bind to nectin-1, nectin-2 and herpesvirus entry mediator (HVEM) receptors, whereas oncolytic viruses based on HSV-1 bind the cells which have 3-O-sulfate modified heparin, HVEM and nectin-1 surface receptors [95]. Of these various oncolytic viruses, HSV-1 based treatments are the most commonly used therapies. Waters *et al*., reported that deactivating insertion of lacZ in UL39, which is known to encode the larger unit of ribonucleotide reductase (RR) of the virus, leads to RR inactivation. This, in turn, enhances the specificity of the virus towards cancer cells (which have a higher level of endogenous RR, thus complementing deficiency of viral RR) and thereby improving the safety of normal cells from the attack of viruses [96]. Nakatake *et al*., also showed both *in vivo* and *in vitro* anti-tumor capability of oncolytic viruses [97]. Moreover, these viruses have shown promising results in the clinical setting and were documented to induce tumor cell death in clinical trials [98]. Alessandrini *et al*., explained the recuperative effect of oncolytic HSV on glioblastoma. They targeted the *ERB-2* human gene by virulent R-115 type of HSV enclosed with murine IL-12. These viruses were used in the murine glioblastoma models and the researchers observed the disappearance of the tumor in approximately 30% of the animals. Since this study revealed promising findings in the treatment of glioblastoma with oncolytic viruses, further clinical evaluation is still under investigation [14].

There are studies that also used the oncolytic viruses with chemotherapies. The combination of different treatments can enhance anti-tumor responses. For example, a combination of ipilimumab and T-Vec is used in Phase Ib trial to treat patients with melanoma. The objective response rate was higher with the combination treatment (39%) compared to the ipilimumab alone (18%). Additionally, the efficacy of the combination of Paclitaxel and T-Vec and the combination of immune checkpoint inhibitors durvalumab and JX-594 has also been examined in clinical trials [99, 100]. In a recent study, the use of a hybrid bacteriophage vector designed for suicide gene therapy with RGD4C/AAVP-Grp78 and its combination therapy with TMZ was investigated. It was seen that tumor-specific Grp 78 promoter of glucose-regulated protein expression was amplified with the help of TMZ and the trans-gene expression of RGD4C/AAVP-Grp78 was also enhanced in glioblastoma. This combination resulted in the suppression of growth in glioblastoma [101]. A study involving rapid angiogenesis mediated by the oncolytic virus (RAMBO), investigated vasculostatin expressing HSV-1 in an *in vitro* and *in vivo* glioma model. Specifically, HSV-1 in combination with bevacizumab, decreased the invasion property of tumor cells *in vitro*. Further, they reported that the size of the tumor was small and the survival rate of the mice was higher in the combination treatment group. In addition to these, RAMBO also decreased the expression of several molecules, which are known to be increased by bevacizumab, such as AKT phosphorylation and cysteine-rich protein 61 (CYR61) [102]. Oncolytic viruses without any genetic alterations combined with reovirus therapy have shown a small increase in the median overall survival of mice with glioblastoma [103]. Based on a large amount of data, a substantial number of oncolytic viruses have reached the platform of clinical trials, however, these oncolytic vaccinations also have some side effects, including nausea, anemia, fever/chills, neutropenia, and thrombocytopenia [98, 104]. Therefore, virus-mediated therapies can be seen as a promising therapeutic option, although there is much to be explored in terms of side-effects and clinical applications.

6. NANO-THERAPIES FOR GLIOBLASTOMA

Nano-technology is a new era in different fields of biological sciences. During the last decade with several technological advancements, nanomaterials have emerged as a po-

tent therapeutic option for glioma (Fig. **3**) [105]. For instance, liposome-based nano-complexes encapsulating wild type p53 plasmid called SGT-53 were investigated in GL-261 glioblastoma model system. These nano-complexes in combination with anti-PD-L1 therapy, enhanced the immune response, inhibited tumor growth and increased intratumoral T cell infiltration in both *in vitro* and *in vivo* studies [50]. Moreover, Seo *et al*., produced a nano-particle that specifically targets miRNA-21, which is an oncogenic miRNA and highly expressed in glioblastoma. They investigated two different delivery systems comprising nano-conjugates around RNA based anti-miRNA-21 conjugated either with cationic poly (amine-co-ester) (PACE) or peptide nucleic acid (PNA). This complex was further accompanied by the block copolymers of poly (lactic acid) and hyperbranched polyglycerol (PLA-HPG). These nano-formulations suppressed the expression of miRNA-21, which led to apoptosis and inhibition of tumor growth. Besides, their combination with TMZ increased chemosensitivity and overall survival in the animal model [106]. The blood-brain barrier (BBB) is an important limiting factor to establish effective treatment for patients with glioblastoma. To overcome this problem, Galstyan *et al*., prepared the biopolymer scaffold, which contained immunoconjugates (NICs) on the nanoscale binding to check-point inhibitors such as PD-1 and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). This nano-biopolymer crossed the BBB and affected the immune cells within the tumor microenvironment in glioblastoma mice models [107]. Similarly, to enhance the efficacy of transportation of the chemotherapeutic drug to the tumor site, Kadiyala *et al*., designed special nano-disc vesicles by mimicking high-density lipoprotein (HDL) that contains a Toll-like receptor 9 (TLR9), CpG and chemotherapeutic agent docetaxel. These vesicles thrived to enter the tumor microenvironment and activate the immune responses through cytotoxic $CD8^+$ T cells. In addition to that, the combination of these nano-discs, which are disc-shaped lipid bilayers of 8-16 nm in diameter, with radiotherapy inhibited tumor progression and increased the survival in *in vivo* glioblastoma models [108]. Similarly, Bastiancich *et al*., used a nano-capsule called Lauroyl-gemcitabine lipid hydrogel ($GemC_{12}$-LNC), which can reach the solid tumors in mouse models. Furthermore, they combined these nano-capsules with Paclitaxel (PTX) for therapeutic use to determine whether they would increase the effect of PTX on tumor compared to PTX alone treatment. They revealed that the combination of PTX-GemC12-LNC enhanced the cytotoxicity in tumor cells. Therefore, the researchers paved a new nano-delivery platform for novel combination therapeutics [16]. Nano-technology can be utilized with some other novel therapeutic approaches. For instance, in a study, researchers showed a novel nano-delivery system named ATN-RNA, which is a polyethyleneimine (PEI) coated magnetic nanoparticle containing double-stranded RNA (dsRNA) in glioblastoma. They reported that this ATN-RNA suppressed its target mRNA, tenascin-C (TN-C) expression and also prevented the migration of tumor cells. This established nano-material also demonstrated high contrast properties on magnetic resonance imaging (MRI) [19]. Zhang *et al*., attempted a combination of nano-material with immunotherapy. They targeted the tumor-associated myeloid cells (TAMCs) and their highly expressed *PD-L1*. They designed an anti-PD-L1 antibody on a lipid nano-particle (LNP), called αPD-L1-LNP. These LNPs decrease the immunosuppressive abilities of TAMCs. Moreover, their combination with radiotherapy enhanced the overall survival in syngeneic CT2A and GL261 glioma mouse models [109]. To summarize, nano-therapies are the precisely targeted drug delivery systems and represent a strong potential to enhance the effectiveness of the current therapeutic approaches for treating glioblastoma.

7. COMBINATION THERAPIES

7.1. Combination of Small Molecule Inhibitors

The infiltrative nature of the glioblastoma exerts resistance to conventional therapies. Therefore, there is a need to develop combinational regimens of different treatments to attain maximum therapeutic benefits. For example, as compared to radiotherapy alone, the combination of radiotherapy with TMZ after surgery leads to a remarkable enhancement in the survival time of patients with glioblastoma [7, 110]. Additionally, the combination of two or more anti-tumor agents having different targets can also become a possible option for treating patients with glioblastoma. For instance, a combination of a tyrosine kinase inhibitor (imatinib mesylate) and microtubule-stabilizing agent (patupilone) showed a better anti-tumor effect in the rat glioma model as compared to either therapy alone [111]. Similarly, the combination of therapeutic agents targeting several receptors such as AEE788 (EGFR and Vascular endothelial growth factor (VEGFR) inhibitor), sorafenib (Ras kinase, VEGFR and platelet-derived growth factor receptor (PDGFR) inhibitor), SU011248 (cKit, VEGFR and PDGFR inhibitor) and ZK222584 or PTK787 (PDGFR and VEGFR inhibitor) may have importance for the treatment, as the amplification or expression of these receptors is altered in glioblastoma. Besides, the combination of inhibitors of various downstream signaling pathways also has the potential for the treatment of glioblastoma. Goudar *et al*., reported that the combination treatment of RAD001 (mTOR inhibitor) and AEE788 led to significant inhibition of tumor growth in the mouse glioma model as compared to either therapy alone [112]. Furthermore, it was reported that the combination of WP1066, a phosphorylated signal transducer and activator of transcription (p-STAT3) inhibitor, and Minocycline prevented the growth of U87 cells [113]. The authors found enhanced expression of a cleaved fragment of caspase 3 showing that the combination of WP1066 and Minocycline led to cell death *via* caspase-dependent apoptosis [113]. On the other hand, the combination of cyclophosphamide and modified vaccine Ankara-5T4 did not enhance the immune response with the addition of the vaccine [114]. In addition, the combination of a VEGFR inhibitor (SU5416) and a direct angiogenesis inhibitor (endostatin) led to a decrease in the growth of tumors in glioma xenograft models as compared to either treatment alone [115].

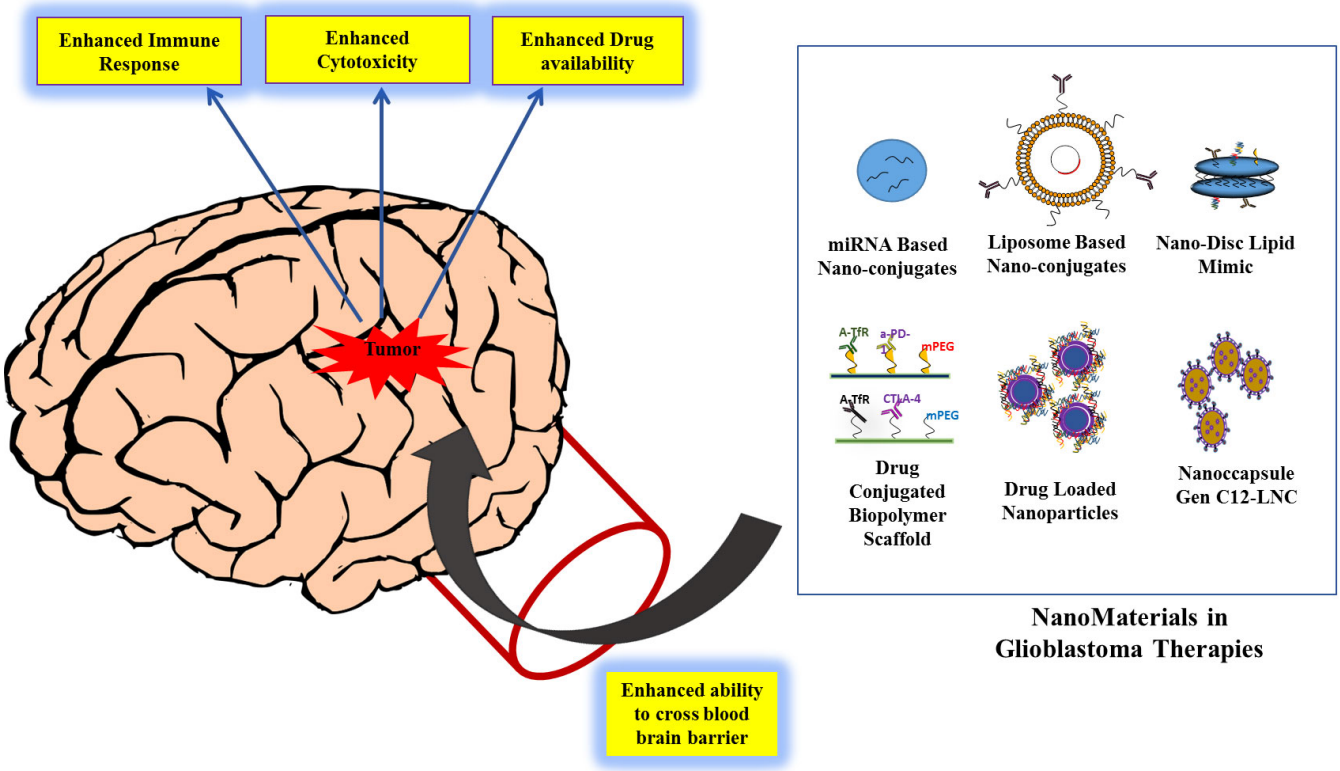

Fig. (3). Schematic representations of novel therapeutic nano-conjugate systems for targeted therapies against glioblastoma. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

7.2. Combination of Small Molecule Inhibitors with Chemotherapies

An additional promising therapeutic option includes the combination of chemotherapy or radiotherapy with targeted molecular therapy. Overexpression of EGFR pathway also led to resistance to the treatment with chemotherapy or radiotherapy [21, 116]. Thus, combining the chemotherapy or radiotherapy with targeted EGFR therapy may enhance the efficacy of the selected treatment. Similarly, the combination of TMZ and thalidomide has been found to be more effective in glioblastoma patients as compared to either single therapy [117]. We investigated the inhibitory potential of genistein in U87 cells. We found that genistein, in combination with Gamma Knife radiosurgery (GKR), enhanced the cytotoxicity and significantly inhibited the p-STAT3 signaling pathway compared with genistein and GKR alone (unpublished data). A combination of low dose TMZ with a COX-2 inhibitor (rofecoxib) showed promising anti-angiogenic activity in glioblastoma patients [118]. In a recent study, TMZ therapy was compared with a combination of Lomustine and TMZ therapy for newly diagnosed glioblastoma patients with methylated MGMT promoter. It was shown that Lomustine and TMZ therapy indeed was more effective compared with TMZ therapy alone; however, further investigations are needed since it was a trial with a small cohort [119]. Similarly, HGF/cMET signaling pathway has been shown to play a crucial role in tumor progression and angiogenesis of glioblastoma [120]. We have investigated the effect of Altiratinib, which is a known inhibitor of tyrosine kinases with cyclophosphamide in U87 and T98 glioblastoma cell lines. Our preliminary *in vitro* findings suggested that the combination treatment effectively inhibited the proliferation of U87 and T98 cells and induced apoptosis. Moreover, this combination also inhibited the expression of MET in both U87 and T98 cells more efficiently compared to Altiratinib alone (Unpublished data). Although combination therapy stands as a potent option for effective therapy, it is crucial to decide the combination partners carefully. In a recent study, the researchers investigated the treatments such as anti-Ang-2/VEGF-A and anti-VEGF-A alone and in combination along with radiotherapy and TMZ in glioma patients. They showed that anti-VEGF-A alone was suitable for combination with radiotherapy; moreover, the combination of anti-Ang-2 and anti-VEGF-A along with chemotherapy presented promising results. Thereby, investigating the underlying complex interactions between drug components in combinatorial therapies is crucial [121]. In another study, Chuang *et al*., used a different combination therapy that included exosomes, which are secreted by glioblastoma-associated macrophages (GAMs), and pacritinib. In this study, they co-cultured the glioblastoma cells with these GAMs and they observed that TMZ resistance of glioblastoma cells was enhanced. They found some responsible factors such as

STAT3, miRNA-21-5p and *SOX2* for chemo-resistance. Also, they reported an increased level of secretion of TGF-β, IL-6 and M2 cytokines in glioblastoma cells. After their treatment with pacritinib, both *STAT3* and *SOX2* were inhibited and stem cell-like properties and tumorigenesis were decreased. Similarly, miRNA-21 levels, which were secreted from GAMs, and M2 cytokine secretion were observed to be decreased [122]. Taken all together, combination therapy showed many advantages since it can target diverse subtypes of cancer cells as well as reduce the systemic toxicity caused by a high dose of single therapy. Therefore, targeting diverse subpopulations of glioblastoma cells could prove a potential therapeutic approach for glioblastoma patients, however, this entails more investigation.

8. CONCLUSION AND FUTURE PERSPECTIVES

The therapeutic advancements for patients with glioblastoma during the last decade have not significantly increased the overall survival. The last most significant breakthrough in the treatment of glioblastoma was the introduction of TMZ together with radiotherapy, which showed some improvement in the survival of the patients. However, recurrence is almost inevitable due to the diffuse and infiltrative nature of glioblastoma and its resistance to the therapies. Moreover, the BBB also represents an obstacle for drug interventions. It is crucial to develop a novel translational therapeutic strategy to address the poor prognosis of patients with glioblastoma. In recent years, we have gained insight into the underlying molecular mechanisms of glioblastoma, which has contributed to the development of new strategies to inhibit tumor growth. Identification of novel molecular targets has become easier with the advent of high throughput sequencing and freely available clinical data along with advanced bioinformatics techniques. Also, targeting the deregulated cellular signaling pathways with small inhibitory molecules or miRNA based gene therapies presents a suitable therapeutic option. The developments in the field of immunotherapies are significant and have attracted the researchers' attention across the globe. One of the major concerns in designing targeted therapy for patients with glioblastoma is the bioavailability of the drug molecule. Surpassing BBB and enhancing drug availability in the tumor can be enhanced *via* nano-drug delivery systems. The implementation of viruses and nanoparticles in enhancing the delivery and transport of novel therapies could be important.

The future of glioblastoma therapeutics is still blooming and unraveling several new dimensions for achieving more targeted and effective treatment strategies. Combinational therapies seem like the best option for treating heterogeneous and aggressive brain tumors such as glioblastoma. Overall, novel targeted therapies in combination with nano-based drug delivery systems could also be a promising treatment option in the future. Further studies are warranted to investigate new therapeutics and particularly combinational therapies for patients with glioblastoma.

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