Disrupted Pathways: Decoding EGFR Mutations and Demographic Inequities in Glioblastoma Progression

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Abstract

Glioblastoma (GB) represents one of the most aggressive treatment-resistant primary brain tumors, with mutations in the Epidermal Growth factor (EGFR) playing a central role in its oncogenic progression. This study synthesizes findings from molecular, in vitro, and population-level analyses to elucidate the mechanisms by which EGFR alterations—particularly the EGFRIII variant— disrupt cellular signaling, DNA repair, and apoptotic regulation. Dysregulation of key modulators, including Mig-6 and Mre-11, was observed to amplify EGFR phosphorylation and activate downstream PI3K/AKT and ARK pathways, thereby promoting tumor proliferation and apoptosis resistance. Additionally, overexpression of MMP-9 was identified as a pivotal factor in metastasis through STAT3/5 and AKT signaling, reinforcing its potential as a diagnostic and prognostic biomarker. Beyond the molecular dimension, this review underscores that populations were age-related physiological decline and socioeconomic barriers contribute to diminished access to care and poorer prognoses. Integrating these molecular and demographic approaches to GB insights highlights the necessity of precision-based and equity-driven approaches to GB diagnosis and therapy. Future directions emphasize the use of proteogenomic analyses, ethical gene-editing strategies, and inclusive clinical design to advance effective, accessible treatment paradigms.

Keywords: Glioblastoma, EGFR, DNA repair, apoptosis, MMP-9, treatment resistance, biomarkers, disparities, demographics

Introduction

Glioblastoma (GBM) is one of the most aggressive and deadly primary brain tumors, known for its rapid progression and poor prognosis. Originating from astrocytes–glial cells that support neurons–GBM can develop in either the brain or spinal cord and often presents with symptoms such as speech difficulties, coordination issues, and seizures, particularly in asymptomatic individuals with no prior neurological history. While the definitive cause of GBM remains unclear, studies suggest that mutations in the patient's DNA (deoxyribonucleic acid), particularly in the *isocitrate dehydrogenase 1 (IDH1)* gene, contribute significantly to GBM development. This mutation promotes neomorphic enzymatic activity, resulting in the production of the oncometabolite 2-hydroxyglutarate, which disrupts epigenetic regulations and supports tumor progression. IDH1 mutations are more frequently observed in secondary glioblastomas that evolve from lower-grade gliomas, compared to primary GBMs, highlighting the need for molecular and histological differentiation during diagnosis [2].

Established risk factors for GBM include aging, exposure to ionizing radiation, and inherited cancer syndromes such as Li-Fraumeni and Lynch Syndrome [1]. While current research has largely focused on the biological mechanisms and therapeutic interventions of GBM, less attention has been given to how non-biological factors–such as age and socioeconomic status– influence disease progression, access to treatment, and survival outcomes [3]. Although extensive work has been done on the tumor’s genetic and clinical characteristics, disparities in care remain a growing concern, particularly among elderly and financially disadvantaged patients [4]. These groups often encounter limited access to high-quality treatment, late-stage diagnoses, and higher rates of comorbidities that complicate care, leading to significantly worse prognosis [5].

This study seeks to critically examine how age-related and socioeconomic barriers affect glioblastoma diagnosis, treatment accessibility, and clinical outcomes. By addressing these often-overlooked disparities, this research aims to contribute to a more equitable understanding of GBM care and support the development of inclusive strategies in clinical practice.

Materials and Methods

This study reviews Glioblastoma (GB) and its varying correspondence to the Epidermal Growth Factor Receptor (EGFR) mutation. This was accomplished through an intricate evaluation of cellular processes such as DNA repair, cell signaling, effects on apoptosis (programmed cell death), and metastatic effects, which were further linked to treatment resistance. Literature was assessed for the purpose of discovering the overall effects of these mutations, which consisted of analyses from pathway and in vivo studies that were utilized to derive results. In addition to this, this study aims to decipher if there lies an interconnection in the onset of GB and its correlation to biomarkers, which can be deemed appropriate to act as effective diagnosis and prognosis indicators for certain demographic populations, such as the elderly and underrepresented groups.

Investigating Glioblastoma (GB) within elderly and underrepresented populations necessitates distinct methodological considerations to capture their unique clinical profiles and address inherent disparities adequately. Studies focusing on elderly GB patients frequently employ age-stratified analyses, comparing treatment responses, toxicity profiles, and overall outcomes across various age cohorts (e.g., 65-75 years, 75+ years) [6]. These methodologies often integrate comprehensive geriatric assessments, which evaluate functional status, burden of

comorbidities, and cognitive function, as these factors are critical determinants of treatment tolerability and prognosis in this vulnerable demographic [6]. For underrepresented groups, including those from lower socioeconomic strata or specific racial/ethnic backgrounds, research methodologies are designed to identify and mitigate disparities in access to specialized care, participation in clinical trials, and diagnostic timeliness [7]. This often involves community-based participatory research approaches, culturally sensitive recruitment strategies, and large-scale retrospective analyses of healthcare databases to identify systemic trends and disparities in care delivery and outcomes [8]. Crucially, for a comprehensive understanding of GB, the collection of biological samples for molecular and genetic analysis must be robust and representative across these diverse demographic groups to ensure that any identified biomarkers or mutation profiles are not biased by patient demographics [9].

Results

Cellular Process

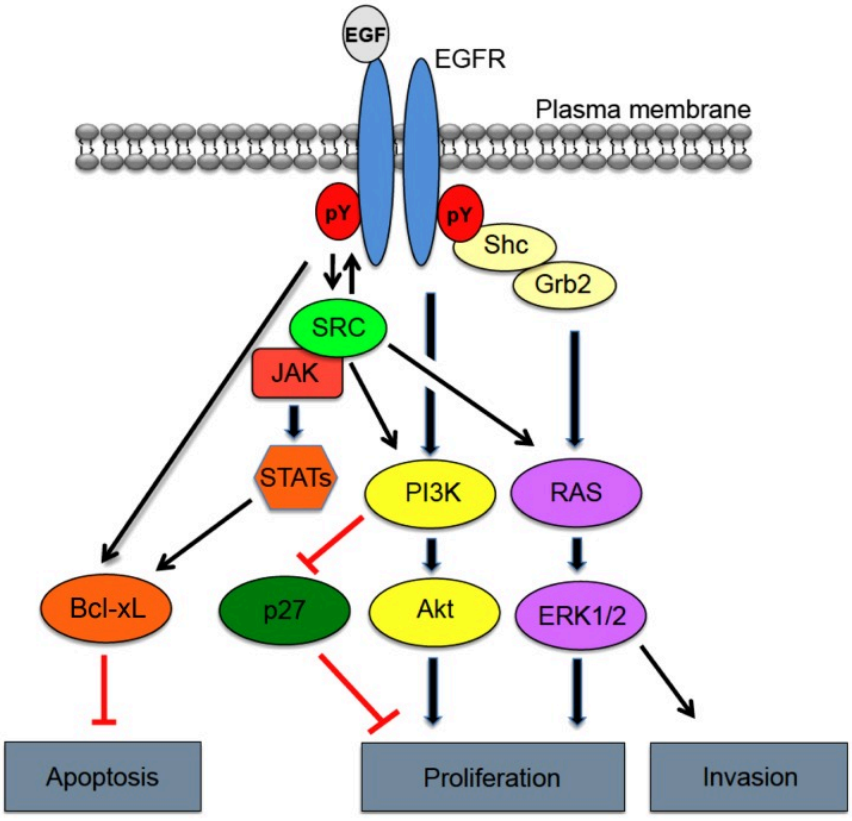

Figure 1. Epidermal growth factor receptor (EGFR) signaling and related pathways in cancer[1].

The epidermal growth factor receptor (EGFR), also known as HER1/ErbB1 and is a member of an extended group of ErbB receptors, which consists of tyrosine kinase activity [10]. From this, a broad range of mutations is present in abundance within malignant health cases, such as GB. This takes place through various forms of ligand-dependent and ligand-independent aspects, such as increased production and receptor protein levels by means of gene amplification. The signals that are communicated from the exterior of the cell to the nucleus are primarily accomplished through SRC, Grb2 (growth factor receptor-bound protein), STAT (signal transducer and activator of transcription), and PI3K (phosphoinositide 3-kinase). Not only this, but this literature has particularly shown a significant upregulated expression of the EGFR mutation within six-tenths of primary glioblastomas, and only one-tenth of secondary glioblastomas, further upholding the representation of the mutation in more common and aggressive forms of GB [10]. The classical forms of GB are characterized by the focal amplification by EGFR, while proneural (essential for neurogenesis), neural, and mesenchymal (associated with embryonic connective tissue) types of GB. The most common type of EGFR mutation, which has resulted in the development of GB, is EGFRΔIII, which takes place from an in-frame deletion of 801 bp within DNA sequencing that encodes the extracellular domain, resulting in the specificity of the mutation being cancer-specific [11].

Effects on DNA and Apoptosis

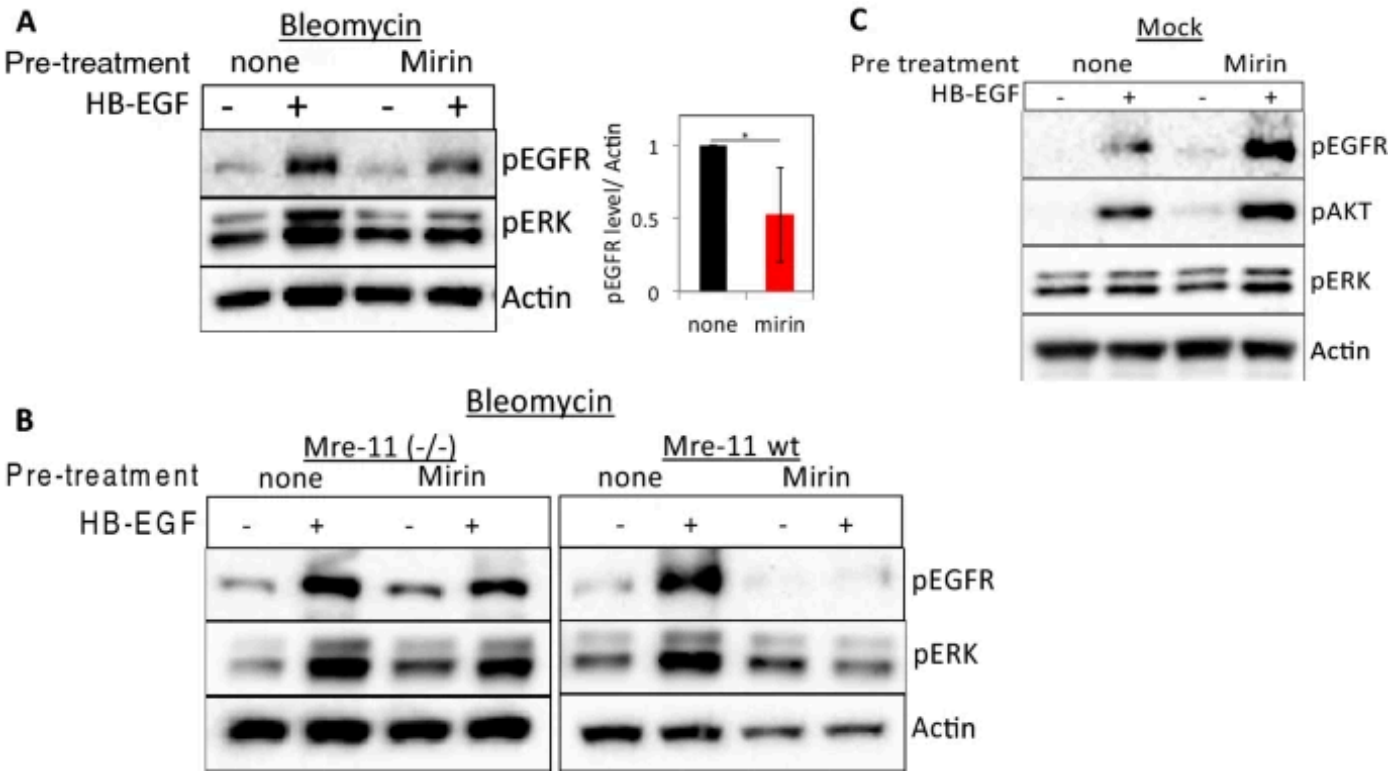

Figure 2. Pharmacological inhibition of Mre-11 interferes with ligand-dependent EGFR signaling in cells suffering from DNA damage[7]

In terms of DNA repair, a study conducted by researchers demonstrated the effects of EGFR through the analysis of normal human dermal fibroblasts (HF) consisting of ATLD2 fibroblasts and ATLD cells alongside wild-type Mre-11 protein [12]. Cells were then manipulated accordingly through bleomycin or hydrogen peroxide for DNA damage. This was then followed by HB-EGF treatment. Antibody arrays and Western blotting were also used to concentrate on EGFR-derived pathways, while flow cytometry was used for the analysis of EGFR surface production, where expression was measured through RNA sequencing and qPCR. Biomarker data were utilized for intricate pathway analysis, and the effects of Apoptosis and proliferation were considered for their importance through the Annexin V and BrdU

incorporation assays, respectively [12]. This study has accommodated the ability of outward signals that are regulated by EGFR on the basis of downstream signaling pathways and its connection to cellular DNA repair capacity [12, 13, 14]. At the same time, the results particularly demonstrated that the expression of Mig-6 (mitogen-inducible gene 6) is diminished, which further contributes to an escalation of EGFR phosphorylation. This process takes place when tyrosine-specific phosphorylation of EGFR leads to binding sites for an adaptor protein, which activates the Ras/Raf/MAPK pathway and ultimately leads to cell proliferation [7, 15]. This correlation of Mig-6 expression by DNA damage exhibits Mig-6 and its role as a cytoplasmic protein that acts as a response-oriented negative regulator of the EGF receptor family. In other words, Mig-6 aids in the prevention of cell growth through the inhibition of EGF receptors following their activation. The knockdown of Mig-6 has contributed significantly to a rise in pEGFR (Y1173), pAKT (phosphorylated protein kinase B), and pERK (phosphorylated extracellular signal-regulated kinase). With more specificity, pEGFR (Y1173) consists of EGFR being phosphorylated (addition of $PO4^{3-}$ to a molecule) in relation to tyrosine 1173, which results in a marker of active EGFR signaling. In addition to this, pAKT contributes to the activity of PI3K/AKT signaling, which is typically seen in anti-apoptotic and cancer-based situations; while pERK corresponds to phosphorylation taking place at Tyr204/Thr202, further leading to kinase activity, whereas an increase in pERK levels is associated with cell proliferation, survival, and differentiation. This can be applied to the metastatic processes of GB, as the restoration of Mig-6 eventually resulted in a downstream signaling pathway and stimulation of EGFR-derived cell signaling. The study also incorporated a favorable pathway which ligand-induced EGFR signaling utilizes to support STAT1 (protein involved in the immune responses of the body), which further adds to metastasized cells and the detrimental effects of apoptosis; while an earlier

study has suggested that the lack of stability within expression levels of Mig-6 in accordance to EGFR leads to the promotion of apoptotic sequences [12]. The study has also shown that the pharmacological restriction of Mre-11 leads to a limitation in EGFR activation for cells that are a byproduct of being exposed to DNA damage. This was accomplished through the evaluation of the effect of mirin on ligand-induced EGFR activation in regular fibroblasts. This resulted in the prevention of HB-EGF-induced phosphorylation corresponding to ERK and EGFR, which were treated with bleomycin. On the other hand, treatment with inhibitors that blocked either DNA-PK (DNA-dependent protein kinase linked to the selective inhibitor of NU7026) or ATM (Ataxia-Telangiectasia Mutated linked to the selective inhibitor of kinase activity) [12].

Metastatic Effects

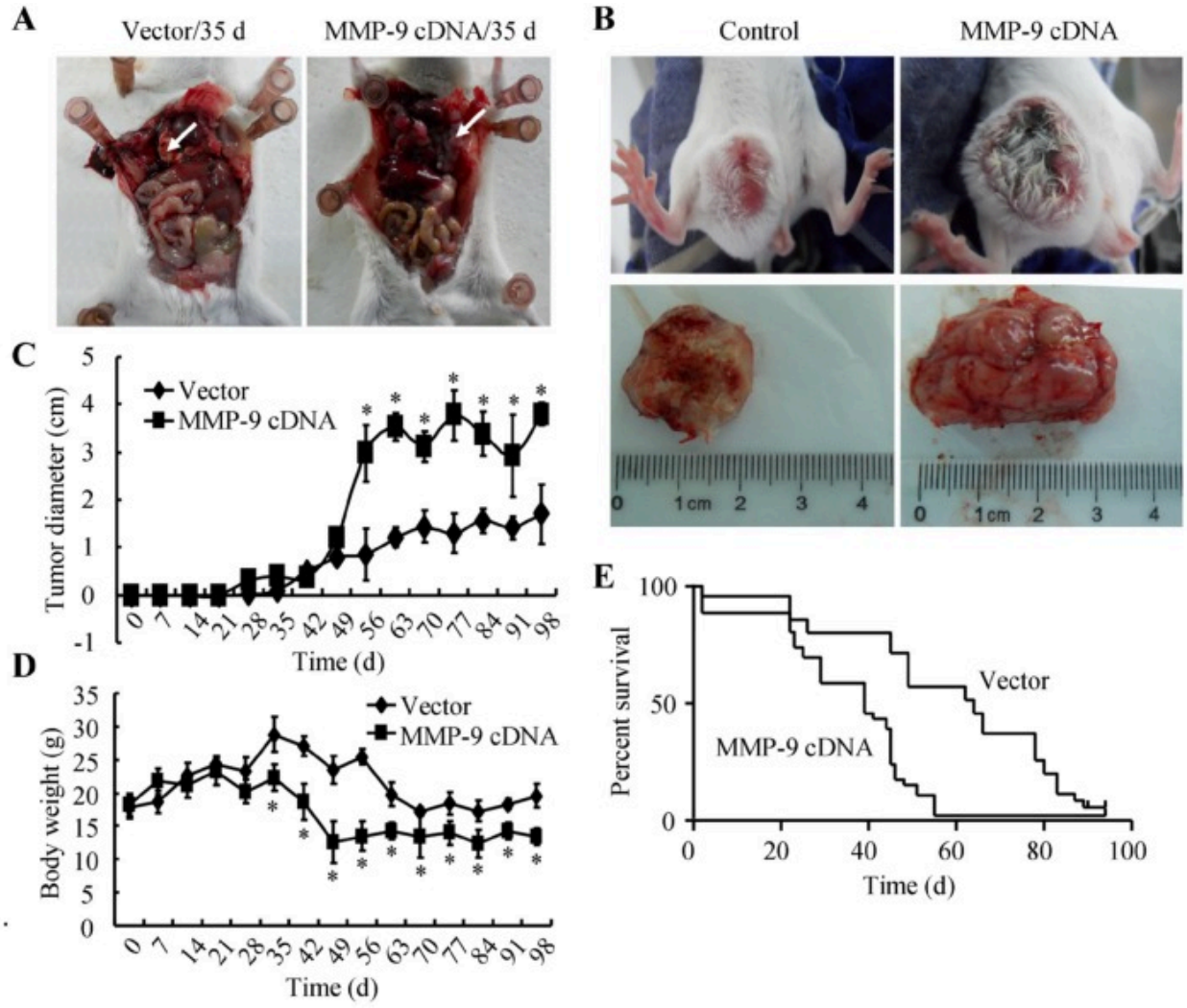

Figure 7. MMP-9 plays critical roles in triggering the metastasis of GBM[11].

When discussing an overall view of the metastatic properties of GB, it is important to understand the interconnectedness of EGF and the EGF receptor (EGFR); however, there are certain aspects that provide limitations in determining the positive and negative effects of the molecular analysis. In this study, A172 GB cells were transfected and cultured with the aid of MMP-9 plasmids or siRNAs, which target the STAT and EGFR proteins. This further resulted in tumor growth and metastasis being determined by mouse models. The study found that the production and activity of MMP-9 (Matrix metalloproteinase-9: enzyme that plays a role within the breakdown of the extracellular matrix) was increased in patients who possessed GBM (glioblastoma multiforme - a common and aggressive form of primary brain tumor within adults, interchangeable with GB); this also paved a technique for researchers to deem MMP-9 as an important biomarker, as MMP-9 significantly diminished in cerebrospinal fluid after operations were conducted. From this, the determination of regulators that affect MMP-9 was done through EGFR, which affects EGF signals through the stimulation of phosphorylation in signaling pathways such as STAT3, STAT5, AKT, and ERK1/2 [13]. To further add validity to the substantial effect which MMP-9 has on glioblastoma-related metastasis, in-vitro studies were conducted where mice were exposed to A172 cells that consisted of MMP-9 cDNa or an empty vector, the cells that were transfected with an increased amount of MMP-9 cDNA resulted in an an overexpression of tumor size, alongside an increase in mortality and decrease in average body weight [13]. Not only this, but the malignant effects of irregular migration, proliferation, and the invasion of cells, which have corresponded to tumor metastasis within the mouse lung.

Analysis of Glioblastoma outcomes consistently reveals significant variations influenced by demographic factors, particularly age and socioeconomic status. Elderly GB patients

frequently exhibit poorer prognoses compared to younger cohorts, often demonstrating reduced tolerance for aggressive standard treatments such as concurrent chemoradiation [14]. This has led to the exploration and implementation of less intensive regimens, including hypofractionated radiation or temozolomide monotherapy, tailored to improve quality of life and manage treatment-related toxicities in this population [15]. Predictive models for elderly patients commonly incorporate factors beyond tumor biology, such as performance status, comorbidity indices, and cognitive function, to more accurately stratify risk and guide treatment decisions [16]. For underrepresented populations, studies consistently report stark disparities in survival rates and access to optimal care [17]. These disparities are often attributed to multifactorial issues, including delayed diagnoses, limited access to specialized neuro-oncology centers, lack of health insurance, and lower rates of participation in clinical trials, which often offer access to novel therapies [16, 17]. These insights underscore that while advancements in understanding tumor biology are vital, the clinical efficacy and real-world outcomes for GB patients are significantly modulated by these demographic and socioeconomic factors, highlighting the need for equitable healthcare delivery.

Discussion

Within society, GB has been evaluated by healthcare professionals and researchers to be one of the most complex and aggressive forms of cancer, which particularly relates to primary GB. The effects that the EGFR mutation can have on GB constitute a network of signal ErbB receptors, along with the STAT transducer and transcription activators, and kinase-based

abnormalities that occur from PI3K. These results are significant as the GB has exhibited oncogenic processes to neural effects, such as resistance to regular and novel targeted therapeutic approaches, the destruction of normal brain tissue, and forms of death [18]. This can identify a prognostic biomarker for the onset of EGFR-targeted therapies and view the mutation through the cellular and molecular alterations that it can cause within the human body. When viewing the effects that EGFR has on apoptosis and DNA repair, it is important to recognize the restriction of Mre-11 (a core component of the MRN complex) and its disruption geared towards ligand-dependent EGFR pathways, particularly for the cells that are familiar with DNA impairments. The cells that exemplify deficient Mre-11 properties coincide with restorations in Mig-6 expression and overall EGFR signaling, where the STAT1 pathway that is upheld by ligand-based EGFR signaling further diminishes the ability for apoptosis to occur, and thus promotes the symptoms of GB through biomarker detection for cancer treatment. The metastatic correlation between the EGFR mutation and GB consists of an abundance of MMP-9 through the activation of several pathways, such as STAT 3/5, AKT, and ERK1/2, which is triggered by EGF via EGFR signaling. This aids in the understanding of the role that MMP-9 can have on certain cells, such as A172, which affects the substantial growth of metastatic tumors. Both of these research studies connect to the means of EGFR having a notable role in the effects of metastasis, apoptosis, and DNA alterations that can serve as diagnostic markers for primary GB.

Limitations and Challenges

The study incorporates Figure 2. Pharmacological inhibition of Mre-11 [7] interferes with ligand-dependent EGFR signaling in cells suffering from DNA damage consists of various research restrictions which may not provide accurate translation to biomarker, diagnostic, and prognostic evaluations. In-vitro constraints are present due to the study being executed only in

normal human dermal fibroblasts (wild-type and Mre-11 (ATLD2) cells), whereas there are a variety of EGFR mutation effects that are absent within fibroblasts. The analysis specifically focuses on Mre-11/Mig-6 and EGFR, while it does not determine the co-mutations or pathway repetitions that can affect tumor cells. The usage of hydrogen peroxide and bleomycin may also lead to challenges in the overall applicability of the study, as these agents will lead to nonspecific and acute DNA lesions, and do not primarily include mutation-based and chronic DNA damage, which is a side-effect of GB tumors. Additionally, no in vivo methodology is utilized to provide confirming validity on the signaling pathways of Mre-11/Mig-6 and its effects on therapy, tumor growth, or DNA alterations. The study specifically provides an exclusive focus on Mre-11 within the DDR networks, and this can contribute to convenience bias in the linked network and provide a lack of importance that other proteins may display. Moreover, the experiment methodology also consisted of early capture time points of 5 to 90 minutes after DNA damage and HB-EGF stimulation, where long-term evaluations were not considered to correlate with chronic effects and long-term therapy options [7].

The study that includes Figure 7. MMP-9 plays critical roles in triggering the metastasis of GBM. This consists of an in-vitro context within the A172 GB cell line on exploring the mechanics of pathways such as ERK1/2, PI3K, AKT, STAT3/5, which was done through cell lines that can be limited in heterogeneity and similarity to tumor microenvironments, which can significantly weaken patient-centered translation. In terms of in vivo methodology through the evaluation of lung metastatic tumors within mice, this does not account for the nervous system (CNS) and blood-brain barrier (BBB) based tumor presence, once again affecting translation of results [18].

Real-world Applications

An important clinical study that coincides with the clinical translation of research regarding the EGFRΔIII mutation is known as the ACT IV study. This analysis focuses on an international double-blind, randomized phase III trial, which was executed across 165 hospitals in 22 countries. The patients who were included within the study had a recent diagnosis of GB and the ability to express EGFRΔIII, while also receiving a maximal surgical removal of the tumor and the completion of standard chemoradiation for the cancer spreading. Patients received standard temozolomide maintenance chemotherapy with either rindopepimut (peptide-keyhole limpet haemocyanin (KLH) vaccine) or control (only KLH) monthly through intradermal injection. As for the results, primary endpoints consisted of overall survival (OS) in patients corresponding to minimal residual disease (MRD) with the tumor being enhanced less than 2 cm^2 after chemoradiation, and the secondary endpoints consisted of OS in a non-MRD subgroup, immune responses, and progression-free survival (PFS). In terms of the statistical significance of the results, the OS for patients with MRD, non-MRD, and PFS was not significantly different from that of the rindopepimut treatment to provide a survival benefit for patients [19]. Despite the utilization of a large-scale study, GB interlinked mutations towards EGFR express treatment resistance to the vaccination. This also negatively affects the immunogenicity and clinical application of patient-centered approaches. Another study focusing on EGFR RNA-based therapies claims that the intratumoral injection of a plasmid or viral vector expressing ΔEGFR-specialized antisense RNA has resulted in a notable lessening of tumor growth; however, the safety of the siRNAs being used as treatment methods provides an enormous concern to the healthcare usability [20].

Future Implications

GB and its interconnectedness to EGFR have prompted an array of novel research methods that must be applied to determine the roles of interlinked mutations, such as EGFRΔIII, and this can result in viewing the condition through a holistic approach, which values biomarkers as a primary indication of the origination and future steps that can be taken for treatment options. There remains a social gap due to the financial barriers that can limit patients' ability to receive treatment methods that suppress GB resistance; thus, rather than focusing on just the introduction of expensive mutation-specific treatments, scalable and community-oriented objectives should also be considered. Not only this, but current research is evolving to provide biomarkers for GB and the genetic mutations associated with it, which can place an emphasis on the need for regular screenings and diagnostic tools that are available to the general public. Fields of study such as proteogenomics can provide insight into translational changes and their cumulative response towards therapeutic resistance, while gene editing through CRISPR can also be ethically utilized to selectively correct or knock out EGFR-linked mutations. However, government intervention should also be prompted through the use of technologies that can provide targeted therapies for the alleviation of symptoms and an increase in prognosis. In terms of systemic studies, the construction of research networks that prompt sufficient collaboration, inclusive of institutions from underrepresented and low-income regions, is of importance, as more privileged research environments can support the enhancement of innovation and implementation. This can be accomplished through the utilization of modern technology in developing datasets and histological cell-sequencing outputs that assist practicing health institutions and public-health initiatives.

The discourse surrounding GB in elderly and underrepresented groups reveals both persistent challenges and critical opportunities for advancing equitable patient care. A significant

advantage is the growing recognition of these populations, which is increasingly driving the development of tailored clinical trials and evidence-based guidelines that account for age-related physiological changes and socioeconomic barriers [21]. However, a substantial limitation remains the persistent underrepresentation of these groups in oncology research, which restricts the generalizability of findings from clinical trials and limits the understanding of how demographic factors interact with disease progression and treatment response [22]. The overarching significance of addressing these disparities lies in achieving equitable outcomes and advancing truly personalized medicine approaches that extend beyond tumor biology to encompass the patient's broader context and social determinants of health [23]. Real-world applications include the development of age-appropriate treatment protocols, the implementation of culturally competent patient navigation programs to improve access to diagnostics and specialized care, and the formulation of health policies aimed at reducing systemic healthcare disparities [24]. Future research endeavors must prioritize the mandatory inclusion of diverse age groups and socioeconomic backgrounds in clinical trials. Furthermore, investigations into how social determinants of health influence the epigenetic landscape, tumor microenvironment, and mutational burden in GB are crucial. This interdisciplinary approach is essential for translating scientific discoveries into tangible improvements in care for all GB patients, ensuring that advancements benefit every individual affected by this devastating disease.

Conclusion

Glioblastoma (GB) remains a significant condition that detrimentally affects individuals due to the effect of the EGFR mutation in correlation to the ErbB receptors. Additionally, the effects of the STAT signal mediator contribute to irregularities that arise from the PI3K enzymes. There has also been a substantial influence on the factors that correspond to Mre-11 and Mig-6 prevalence. MMP-9 has also been shown to be linked with numerous pathways, such as STAT3/5, AKT, and ERK 1/2. Furthermore, the manifestation of EGFR with GB has been linked to the utilization of siRNAs as treatment options. Despite this, there remain social factors such as financial status connected to the cost of treatment. This can be alleviated through the prevalence of community events and continuous screening and diagnostic methods, which are utilized as biomarker screeners. The usage of histology also shows promise in the collaboration between the government and healthcare institutions, where low-income regions can be associated with other areas for medical assistance. In terms of the effect of GB on elderly and marginalized groups of individuals, research has shown promise through the personal analysis of medication requirements for each patient in terms of societal factors, which consider culture, age, accessibility, clinical trials, and health policies. This contributes to the long-term perspective of GB being a condition that can be offset with mutations and biomarker-relevant research, which is interlinked with crucial priorities of certain groups.

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