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RESEARCH ARTICLE

Glioblastoma Multiforme: A Review of the Genetic Alterations

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ABSTRACT: Glioblastoma Multiforme is a neurological disease resulting from many genetic mutations. In the presence of Glioblastoma Multiforme patients are presented with a short period after their prognosis as this form of glioma is a stage 4 tumor, and it is also considered the most defective of the neurological tumors. This review article examines the multiple genetic alterations that occur because of the uncontrollable reproduction of the glioblastoma multiforme tumor cells in the nervous system. Previous experiences and studies discussed singular gene mutations in Glioblastoma Multiforme. However, the reason these specific mutations occur, their advantages for the disease, and the normal function of the unmutated genes still need to be fully uncovered. In my review article, I found that Glioblastoma Multiforme is a very invasive form of cancer that occurs because of many genetic mutations. The mutations will also provide information about potential therapeutic strategies to eradicate the disease from patients.

KEYWORDS: Genetics, Glioblastoma Multiforme; Gliomas; Genetic Alterations; Amplifications; Mutations Deletion.

Introduction

Prevalent in 45.2% of adults with brain and central nervous system tumors, glioblastoma multiforme is an incurable form of a primary brain tumor. In previous years, the disease affected 3.21 people in a population of 100000 people.[1] This irremediable disease can provide the affected person with a median survival period of 15 months after diagnosis, as only 5.5% of patients can survive past 5 years. The malignancy, high mitotic activity, and necrosis caused this neurological disease to be classified as a stage 4 cancer. GBM can present itself in primary and secondary forms, which contrast with one another. Primary GBM presents itself in older patients with an average age of 62, whereas secondary GBM presents itself in patients with a younger average age of just 45 years.[2,3]

Furthermore, many genetic alterations and pathways vary between the two forms of this disease, causing them to contrast. This disease can blend in by appearing as normal neurogenesis and central nervous system cells, allowing it to affect receptor-Ras and signaling pathways. GBM affects the signaling pathways in cell proliferation, survival, and DNA synthesis.[4,5]

This neurological disease has a unique ability to blend as it can modify gene expression without changing the DNA sequence. These modifications cause epigenetic alterations in the mechanisms such as DNA methylation, histone modifications, chromatin remodeling, and noncoding RNA expression.[6] All these epigenetic mechanisms play a key role in cells and are crucial for creating tumours.[6] Glioblastoma multiforme or gliomas also cause many genetic alterations, leading to the formation and progression of tumours.[4,5]

This review paper will further discuss Glioblastoma multiforme and its genetic alterations. Even though the genetic alterations will not be discussed in depth about the various forms of GBM, they will be addressed holistically concerning both variations. Each genetic alteration will be accompanied by a figure utilized to further understand the modification's scope. This review article will also delve into the therapeutic strategies for treating this disease based on articles from PubMed and other scholarly resources.

Discussion

Both primary and secondary gliomas have different genetic variances. Primary GBM causes EGFR amplifications, mutation of chromosome 7p, homozygous deletion of the CDKN2A-p16INK4a gene in the 9p chromosome, and PTEN gene deletion, which also occurs with monosomy 10.[7] However, unlike primary GBM, secondary glioblastoma multiforme causes TP53 mutations on chromosome 17p and infrequent PTEN alterations.[7] Even though secondary GBM is also a type of stage 4 cancer, it also has genetic mutations in the IDH1/2 genes, which are characterized by low-grade glioma.[8] Unlike secondary, primary also depicts characteristics that are present in high-grade glioma, these include NF1, PKJ3R1, PIK3CA, and PDGFRA/B amplifications.[9] Additionally, many other genetic alterations occur, which cause this disease to be as prevalent as a stage 4 cancer.[4,5]

Epidermal Growth Factor Receptor:

EGFR is a 200kb gene that can encode a protein consisting of 1210 amino acids. Located on the shorter arm of the 7th chromosome, it is overexpressed in various cancers including Glioblastoma Multiforme. The epidermal growth factor receptor normally triggers cell growth, development, and differentiation. However, this receptor sends irregular signals in mutated cells that cause carcinogenesis.[10] Similarly, the EGFR gene is overexpressed in 60% of the more effective primary GBM, whereas it is only prevalent in 10% of the secondary GBM.[11] This significant difference between the two types of neurological disease is due to this characteristic's aggressive nature. Furthermore, it has been determined by the TCGA database that 57% of GBMs cause the frequent activation of EGFR due to the gene mutations and amplifications they enfold.[12]

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The severe effects of this mutated gene arise with the alterations in the genetic sequence. A significant alteration that allows the tumor to gain therapeutic resistance is EGFRΔIII.[13] As a result of removing the 801 bp from the extracellular domain's DNA sequence using the aa 6-273 deletion, EGFR fabricates of a short-living, overactive, extensively generated variant of the receptor.[13] Even though this mutation can provide the GBM cells survival *in vivo* by enhancing the mitogenic factors,[14] its imperceptibility allows it to be a frequently targeted characteristic for therapeutic intervention.

Furthermore, EGFRΔIII is vital in glycogenesis as it has transformative properties that cause the augmentation of astrocytes with exhausted INK4A/Arf and neural stem cells that can create high-grade tumors *in vivo*.[15] This infinitesimal mutation is resilient to chemotherapy and radiotherapy and is essential in GBM because it can initiate tumors when it is paired with the GSC marker CD133+.[16] Due to the mutation's severe nature and over-amplification of the EGFR, the patient is provided with a poor survival prognosis.[16]

Even though EGFRΔIII is a significant mutation that occurs to the EGFR gene in the Glioblastoma multiforme, it is not the only mutation that occurs in this coding region, as proven by a sequence analysis of 151 glioblastoma tumours.[17] R198K, T263P, A289V, 5598V, and L861Q are missense mutations that can be employed as a hyperphosphorylated version during the absence of a ligand and cause the over-representation of the EGFR gene.[18]

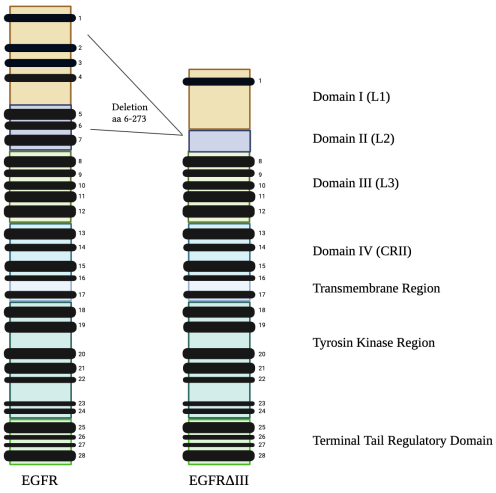

Figure 1: An image of the aa 6-273 deletion causing a variation in the EGFR gene to produce EGFRΔIII. Additionally, the sections of the EGFR gene are labeled with their corresponding names and segregated by color.

Isocitrate Dehydrogenase 1:

Located near the enzyme's active site, the IDH1 gene is converted into the IDH1R132H variant with the mutation of the genetic sequence of codon 132. This minute mutation of a singular codon causes the creation of a histidine amino acid instead of arginine.[19] IDH1 is a catalyzer that aids with the forming of alpha-ketoglutarate from the oxidative carboxylation of isocitrate. However, its most recurrent job is its ability to reduce NADP into NADPH. Due to its significant roles in intracellular processes, the IDH1 gene is habitually mutated patients.[21] This variated version of the IDH1 gene causes the gene to gain an oncogenic function that results in genome-wide methylation due to the conversion of alpha-ketoglutarate into oncometabolite 2-hydroxyglutarate.[20]

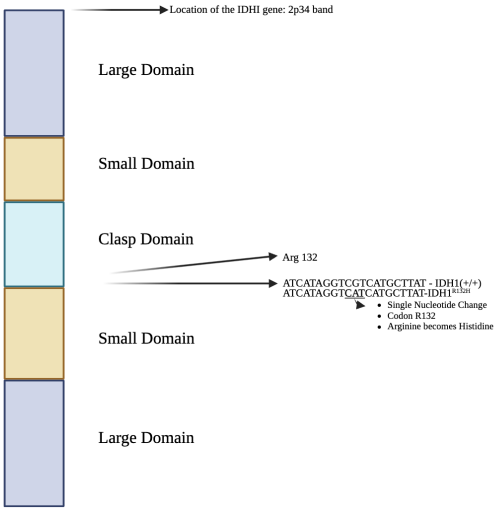

Figure 2: An image portraying the single nucleotide polymorphism that causes the creation of histidine instead of arginine. The gene is depicted to the left with labeled sections segregated with color. Additionally, the base sequence change is shown on the right.

Even though, IDH1R132H results in the creation of oncogenic properties, it provides patients suffering from GBM with a progenesis with a higher life span than normal IDH1.[22] Furthermore, its significant prevalence in secondary GBMs allowed this mutation to be defined as a definitive marker for this variant of the neurological disease.[19] Additionally, this unique capability of this recurring alteration may allow for the creation of therapeutic strategies for combating Glioblastoma Multiforme.[19] Unlike EGFR mutations, IDH1R132H is a gene whose alterations are easily detectable in Glioblastoma Multiforme, allowing it to be a biomarker for this disease.[21]

Neurofibromatosis Type 1:

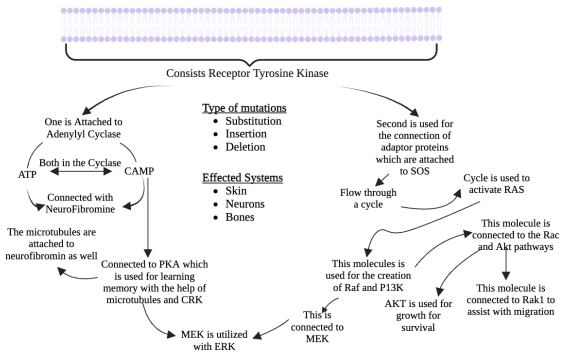

Figure 3: An image depicting the mutation pathways for the Neurofibromatosis Type 1. Additionally, it is accompanied by a list of the types of mutations that occur on this gene and the types of systems that are affected by these mutations.

Neurofibromatosis Type 1 is a 280 kb gene that encodes for the protein neurofibromin and is located on chromosome 17q11.2.23 The gene that consists of 3 or more alternative spliced exons and 57 constitutive exons.[24] Furthermore, NF1

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can complicate molecular diagnosis due to its pseudogenes on chromosomes 2, 12, 14, 15, 18, 21, and 22. NF1 is particularly used in cells as a cell cycle regulator and tumor suppressor.[25] So, this gene oversees the cell cycle, the replication period, and the growth rate to prevent cells from excessively reproducing and mutating.[26] However, in GBM, this gene is deleted, causing the excessive reproduction of the mutated tumorous cells.[27]

Furthermore, in 13 – 14 % of GBM patients, NF1 is mutated[27] due to this gene's frameshifts, single nucleotide polymorphisms, and splice variants. This gene can be mutated into many forms all of which cause the abbreviation neurofibromin and nonsense-mediated ribonucleic acid decay. Even though the prevalence of this mutation for neurological disease is particularly low compared to the other mutations, this disease provides the patient with a very low survival chance. Additionally, this gene's inability to function or delete causes astrocyte mutations. This causes the increase of astrocyte proliferation, and they cause the overactivation of KRAS instead of HRAS.[28]

Tp53:

Furthermore, in 13 – 14 % of GBM patients, NF1 is mutated[27] due to this gene's frameshifts, single nucleotide polymorphisms, and splice variants. Located on chromosome 17p13.1, TP53 is a gene that encodes p53, a protein consisting of 393 amino acids.[29] Under normal conditional, p53 functions as a transcriptional factor with a nucleotide-binding domain that complies with the consensus DNA sequence of the protein and other domains that can communicate with regulatory pathways while regulating transcriptional activity.[30] Although this protein has extensive functions, it has comparatively low activity, which MDM2 and MDM4 regulate.[31] This regulatory interaction is diverted when p53 is inducted due to the stress signals produced by damaged DNA. After its induction, the protein prevents the damaged cells from replicating by producing cell cycle arrest, senescence, and apoptosis.[32]

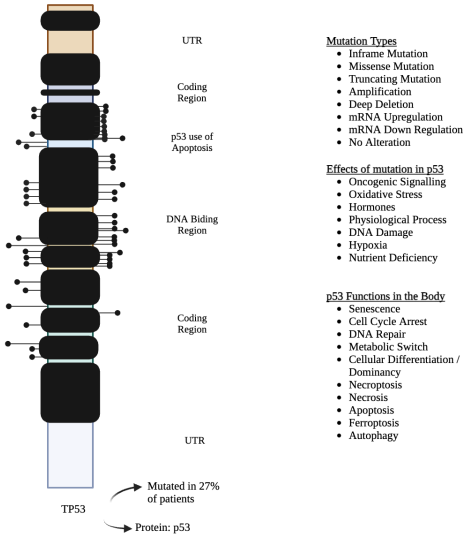

Figure 4: The image depicts the frequency of the genetic mutation at specific portions of the TP53. Using the lines, the frequency of the mutations is shown. Moreover, this image also represents the mutation types that occur on this gene. Additionally, the type of effects of these mutations and the corresponding protein's functions are also depicted in this image.

PTEN:

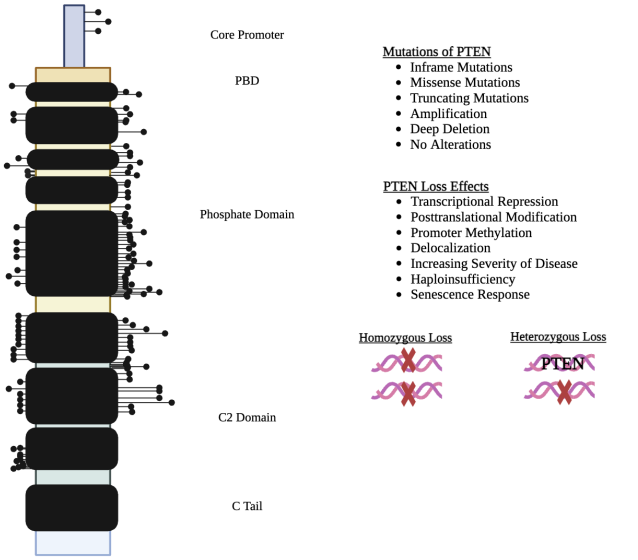

Figure 5: The image depicts the frequency of the mutations at a specific part of this gene using line length. It also represents the names of specific parts segregated by color. Moreover, the types of loss, the PTEN loss effects, and the types of mutations that occur to this gene are all depicted in the lists on the right side of the image.

Enzyme phosphoinositide 3 kinase produces the second messenger phosphatidylinositol 3,4,5 triphosphate, with the assistance of the enzyme activating the tyrosine kinase pathway.[33] Once the second messenger has been produced, it is inactivated using the PTEN catalyzer.[33] However, this process does not occur with the presence of glioblastoma multiforme because this neurological disease causes hemizygous or homozygous deletions in nearly 90% of the patients.[34] So, since there is a lack of inactivation for the second messenger and a depletion of PTEN, the P1 3-kinase pathway receives increased signalling.[33] Furthermore, the deficit of PTEN also affects a maintenance protein for undifferentiated GBM tumor-initiating cells because it causes this Lg11 protein to be inactivated.[35]

PTEN is a protein that is functional due to epigenetic, transcriptional, and post-translational processes, and it is a regulator for tumor sensitivity in patients receiving therapy.[36] However, with the presence of GBM, PTEN is deleted or mutated to prevent the tumor from being affected by the protein's tumorigenesis-controlling features.[37] There are many disadvantages to GBM development with the presence of PTEN because this protein causes the tumor to be more susceptible to therapy, decreases the malignancy of the tumor cells, and impairs glycolysis inhibition for GBM metabolism.[37]

Therapies (expand on the therapies description):

Glioblastoma Multiforme is one of the hardest tumors to treat because the neurological disorder poses challenges to conventional treatments due to its heterogeneity, behavior, and improbability.[38] Since this disease is so unpredictable, many specific therapeutic measures have been developed, including the enhancing anti-cancer immune response and destroying tumor cells.[3] The appropriate treatment option depends on many factors, including the patient's symptoms, physicality,

and the tumor's effectiveness.[3] Even though these factors play into account, the main requirements of the treatments are to eradicate the tumorous cells, decrease the potential effect of the treatments, bring back the function of the affected parts, and stop metastasizing tumors from being created.[3] Many potential treatments could occur, such as surgery, chemotherapy, radiation therapy, virotherapy, immunotherapy, gene therapy, and epigenetic therapy.

Gene therapies are enstated with the alteration and editing of specific genes that cause the creation of cancerous cells.[39] This therapy is caused by the restoration of tumor suppressor genes that have been deleted and the extraction or slicing of oncogenes.[39] In previous treatments, the whole genome was edited to prevent cancer. Still, with current emerging treatment approaches, genes are altered, inserted, removed, and modulated to decrease the spread of the cancer.[40]

Oncogene Silencing:

The main process in this therapeutic measure occurs when nucleic acid is injected into tumor cells to eradicate the expression of certain genes.[41] Since this disease is propelled by the overexpression of many genetic alterations and proteins, nucleic acid acts as a countermeasure to deplete the expression by silencing them to reduce the spread and effectiveness of GBM.[42] Oncogenic silencing can occur with small interfering RNA (siRNA). However, there is no effective method to transport the siRNA to the region silencing. Even though some carriers have been discovered to transport this form of RNA, there have only been a few successful cases in which these carriers have shown promising results.[43]

Suicide Gene Therapy:

Suicide gene therapy is a method that is utilized to immobilize and decrease the viability of the cancerous Glioblastoma Multiforme cells.[44] The cells are affected by the introduction of toxin genes or cytotoxic proteins, both of which are used to destroy the effectiveness of the neurological disease's cells.[44] Moreover, there are many methods to incorporate this method including employing of mesenchymal stem cells.[45] In this treatment, the stem cells that are genetically engineered are injected with nuclei that contain the suicide gene TGF-B.[46] Another method for suicide gene therapy involves the embodiment of viral vectors, which are used to insert the herpes simplex virus thymidine kinase.[47]

Targeting Angiogenesis:

Using angiogenesis to eradicate glioblastoma multiforme's tumorous cells involves two different strategies.[48] These strategies encompass angiogenic factors but are used in various methods because the anti-angiogenic factors are overexpressed, and the pro-angiogenic factors are under-expressed.[44] This treatment involves inhibiting the growth of blood vessels which reduces the growth of the tumors due to the lack of food and the build-up of toxic waste.[49]

Targeting tumor cell–derived exosomes:

Proteins, DNA and RNA are all part of extracellular nanovesicles used for intercellular communications and they are called called exosomes.[50] Even though the exact macromolecules in the exosomes vary with the type of cells, they are usually crucial for tumor development as they are secreted in higher quantities in tumorous cells.[51] Since exosomes are important for intercellular commutations, stem cells with glioblastoma that contain exosomes with microRNA have been used for treatment.[52] These microRNAs are useful because they provide intercellular and extracellular communications.[52]

Immunization gene therapy:

Cytokine gene therapy, tumor vaccine therapy, and chimeric antigen receptor T cells are various methods used to improve the immune system of patients suffering from glioblastoma multiforme.[53] Since this type of therapy is vague, this treatment mainly focuses on ameliorating the immune system to combat the tumorous cells that are presented with the neurological disorder.[53] These treatments usually include mutated mRNA to combat the disease. Additionally, they do not have many extensive side effects as they are like the COVID–19 vaccines.[54]

Tumor gene repair:

Tumorigenesis involves the abnormal delineation of DNA repair genes known for their roles in the progression of glioblastoma multiforme cells.[55] However, the repair of tumorous cells is complex as it only embodies the genetic alteration of specific tumor-causing genes in the damaged genome.[56] This process helps repair the tumorous genes and allows for the discovery of resistance to genotoxic therapies derived from tumor-driving cells.[56]

Genome Editing:

Genome editing uses substitution, insertion, deletion, or integration to modify the whole-body intracellular DNA sequence.[57] This method for eradicating tumorous cells uses an immense amount of technology as it can potentially employ CRISPR/Cas9 systems.[57] However, it provides the opportunity to repair specifically affected sections of the DNA to reduce the production of cancerous cells. Moreover, this form of treatment can be used on somatic cells and germline cells, which are both for reproduction and not for reproduction.[58]

■ Conclusion

This review article was created to provide the reader with a detailed explanation of certain genetic alterations in Glioblastoma Multiforme. Moreover, these genetic alterations are discussed, including the mutations that occurred, their effect on the patient, and their capabilities in tumorigenesis. In addition, the mutations in neurological disease are accompanied by figures that give the reader a visual representation of the content. The review article also discusses the treatments that are available for the eradication of Glioblastoma Multiforme. This topic can be further addressed by depicting the other genetic alterations that neurological diseases can create. Also, GBM can be further discussed with research on different types of alterations and therapies that are not completely related to genetics. As stated in the review article, many potential alterations and therapies can be created and used for GBM, and the genetic portion is only a small part of GBM. However, using images and detailed descriptions of the main effects of gene alteration in this research article makes it distinct from the other articles about this glioma. Finally, future research for this disease should also focus on reducing the symptoms of the disease to allow patients to have a fuller life. Additionally,

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the researcher for this disease should also research the process of initiation for the mutation that occurs to discover potential methods to stop the creation of the alterations. Moreover, the article's ability to discuss the specific mutations that cause this creation and treatments to prevent the spread allows this research article to provide the reader with a deep understanding of Glioblastoma Multiforme.

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References

1. Prabhu, Vikram C. "Glioblastoma Multiforme." *AANS*, www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme. Accessed 17 Feb. 2024.
2. Tejaswi Kanderi, and Vikas Gupta. "Glioblastoma Multiforme." *Nih.gov*, StatPearls Publishing, 12 Sept. 2022, www.ncbi.nlm.nih.gov/books/NBK558954/. Accessed 3 Aug. 2023.
3. Gupta, Nidhi, *et al*. "Cost-Effectiveness of Temozolamide for Treatment of Glioblastoma Multiforme in India." *JCO Global Oncology*, no. 7, 1 Dec. 2021, pp. 108–117, pubmed.ncbi.nlm.nih.gov/33449801/, https://doi.org/10.1200/go.20.00288. Accessed 26 Aug. 2023.
4. Crespo, Inês, *et al*. "Detailed Characterization of Alterations of Chromosomes 7, 9, and 10 in Glioblastomas as Assessed by Single-Nucleotide Polymorphism Arrays." *The Journal of Molecular Diagnostics*, vol. 13, no. 6, 1 Nov. 2011, pp. 634–647, www.sciencedirect.com/science/article/pii/S1525157811002261, https://doi.org/10.1016/j.jmoldx.2011.06.003. Accessed 26 Aug. 2023.
5. Crespo, Inês, *et al*. *Molecular and Genomic Alterations in Glioblastoma Multiforme*. Vol. 185, no. 7, 1 July 2015, pp. 1820–1833, www.sciencedirect.com/science/article/pii/S0002944015001972, https://doi.org/10.1016/j.ajpath.2015.02.023. Accessed 3 Aug. 2023
6. Jones, Peter A, and Stephen B Baylin. "The Epigenomics of Cancer." *Cell*, vol. 128, no. 4, 1 Feb. 2007, pp. 683–692, www.sciencedirect.com/science/article/pii/S0092867407001274, https://doi.org/10.1016/j.cell.2007.01.029. Accessed 26 Aug. 2023.
7. "Scopus Preview - Scopus - Document Details - Molecular Genetics of Gliomas." *Scopus.com*, 2014, www.scopus.com/record/display.uri?eid=2-s2.0-84893519542&origin=inward&txGid=775f70267006bcbefa193fbe6dca0a7f. Accessed 26 Aug. 2023.
8. Christensen, Brock C, *et al*. "DNA Methylation, Isocitrate Dehydrogenase Mutation, and Survival in Glioma." *Journal of the National Cancer Institute*, vol. 103, no. 2, 19 Jan. 2011, pp. 143–153, academic.oup.com/jnci/article/103/2/143/2568867, https://doi.org/10.1093/jnci/djq497. Accessed 26 Aug. 2023.
9. "An Integrated Genomic Analysis of Human Glioblastoma Multiforme." *Science*, 2023, www.science.org/doi/10.1126/science.1164382. Accessed 26 Aug. 2023.
10. Vladimir Jurišić, *et al*. "Epidermal Growth Factor Receptor Gene in Non-Small-Cell Lung Cancer: The Importance of Promoter Polymorphism Investigation." *Analytical Cellular Pathology,* vol. 2018, 14 Oct. 2018, pp. 1–9, www.ncbi.nlm.nih.gov/pmc/articles/PMC6204164/#:~:text=EGFR%20is%20located%20at%20
11. Huang, Paul H, *et al*. "Oncogenic EGFR Signaling Networks in Glioma." Science Signaling, vol. 2, no. 87, 8 Sept. 2009, pubmed.ncbi.nlm.nih.gov/19738203/, https://doi.org/10.1126/scisignal.287re6. Accessed 12 Aug. 2023.
12. Brennan, Cameron, *et al*. "The Somatic Genomic Landscape of Glioblastoma." Cell, vol. 155, no. 2, 1 Oct. 2013, pp. 462–477, www.ncbi.nlm.nih.gov/pmc/articles/PMC3910500/, https://doi.org/10.1016/j.cell.2013.09.034. Accessed 10 Aug. 2023.
13. Wong, Albert J, *et al*. "Structural Alterations of the Epidermal Growth Factor Receptor Gene in Human Gliomas." *Proceedings of the National Academy of Sciences of the United States of America*, vol. 89, no. 7, 1 Apr. 1992, pp. 2965–2969, www.ncbi.nlm.nih.gov/pmc/articles/PMC48784/?page=3, https://doi.org/10.1073/pnas.89.7.2965. Accessed 12 Aug. 2023.
14. Nagane M;Coufal F;Lin H;Bögler O;Cavenee WK;Huang HJ. "A Common Mutant Epidermal Growth Factor Receptor Confers Enhanced Tumorigenicity on Human Glioblastoma Cells by Increasing Proliferation and Reducing Apoptosis." *Cancer Research*, vol. 56, no. 21, 2022, pubmed.ncbi.nlm.nih.gov/8895767/. Accessed 12 Aug. 2023.
15. Bachoo, Robert, *et al*. "Epidermal Growth Factor Receptor and Ink4a/Arf." *Cancer Cell*, vol. 1, no. 3, 1 Apr. 2002, pp. 269–277, www.cell.com/cancer-cell/fulltext/S1535-6108(02)00046-6, https://doi.org/10.1016/s1535-6108(02)00046-6. Accessed 12 Aug. 2023.
16. Heimberger, Amy B, et al. "Prognostic Effect of Epidermal Growth Factor Receptor and EGFRvIII in Glioblastoma Multiforme Patients." *Clinical Cancer Research*, vol. 11, no. 4, 15 Feb. 2005, pp. 1462–1466, aacrjournals.org/clincancerres/article/11/4/1462/188834/Prognostic-Effect-of-Epidermal-Growth-Factor, https://doi.org/10.1158/1078-0432.ccr-04-1737. Accessed 12 Aug. 2023.
17. Lee, Jeffrey C, *et al*. "Epidermal Growth Factor Recoblastoma through Novel Missense Mutations in the Extracellular Domain." *PLOS Medicine*, vol. 3, no. 12, 19 Dec. 2006, pp. e485–e485, journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0030485, https://doi.org/10.1371/journal.pmed.0030485. Accessed 12 Aug. 2023.
18. Raizer, Jeffrey J, *et al*. "A Phase II Trial of Erlotinib in Patients with Recurrent Malignant Gliomas and Nonprogressive Glioblastoma Multiforme Postradiation Therapy." *Neuro-Oncology*, vol. 12, no. 1, 14 Dec. 2009, pp. 95–103, academic.oup.com/neuro-oncology/article/12/1/95/1103486, https://doi.org/10.1093/neuonc/nop015. Accessed 12 Aug. 2023.
19. Dang, Lenny, *et al*. "IDH Mutations in Cancer and Progress toward Development of Targeted Therapeutics." *Annals of Oncology,* vol. 27, no. 4, 1 Apr. 2016, pp. 599–608, www.sciencedirect.com/science/article/pii/S0923753419357643, https://doi.org/10.1093/annonc/mdw013. Accessed 12 Aug. 2023.
20. Polivka, Jiri, *et al*. "IDH1 Mutation Is Associated with Lower Expression of VEGF but Not Microvessel Formation in Glioblastma Multiforme." *Oncotarget*, vol. 9, no. 23, 20 Feb. 2018, pp. 16462–16476, www.oncotarget.com/article/24536/text/, https://doi.org/10.18632/oncotarget.24536. Accessed 12 Aug. 2023.
21. "Scopus Preview - Scopus - Welcome to Scopus." *Scopus.com*, 2023, www.scopus.com/home.uri. Accessed 12 Aug. 2023.
22. Miyata, Nozomu, *et al*. *A Flexibly Grasping and Manipulating Mechanism Composed of Many Elastic Cords — Posture Control of Grasped Object*. 1 Oct. 2019, ieeexplore.ieee.org/document/8932136, https://doi.org/10.1109/icmect.2019.8932136. Accessed 12 Aug. 2023.
23. Viskochil, David, *et al*. "Deletions and a Translocation Interrupt a Cloned Gene at the Neurofibromatosis Type 1 Locus." *Cell*, vol. 62, no. 1, 1 July 1990, pp. 187–192, pubmed.ncbi.nlm.nih.gov/1694727/, https://doi.org/10.1016/0092-8674(90)90252-a. Accessed 13 Aug. 2023.
24. Mirjam Luijten, *et al*. "Mechanism of Spreading of the Highly Related Neurofibromatosis Type 1 (NF1) Pseudogenes on Chromosomes 2, 14 and 22." *European Journal of Human Genetics*, vol.

8, no. 3, 1 Mar. 2000, pp. 209–214, www.nature.com/articles/5200434, https://doi.org/10.1038/sj.ejhg.5200434. Accessed 13 Aug. 2023.

25. "Progress and Challenges in Developing a Molecular Diagnostic Test for Neurofibromatosis Type 1." *Expert Review of Molecular Diagnostics*, 2014, www.tandfonline.com/doi/full/10.1586/erm.11.52. Accessed 13 Aug. 2023.
26. "NF1 Gene: MedlinePlus Genetics." *Medlineplus.gov*, 2023, medlineplus.gov/genetics/gene/nf1/#:~:text=Neurofibromin%20acts%20as%20a%20tumor,stimulates%20cell%20growth%20and%20division. Accessed 13 Aug. 2023.
27. Cerami, Ethan, *et al.* "The CBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data." *Cancer Discovery*, vol. 2, no. 5, 1 May 2012, pp. 401–404, aacrjournals.org/cancerdiscovery/article/2/5/401/3246/The-cBio-Cancer-Genomics-Portal-An-Open-Platform, https://doi.org/10.1158/2159-8290.cd-12-0095. Accessed 13 Aug. 2023.
28. Anastasaki, Corina, et al. "Updated Nomenclature for Human and Mouse Neurofibromatosis Type 1 Genes." *Neurology Genetics*, vol. 3, no. 4, 26 July 2017, pp. e169–e169, ng.neurology.org/content/3/4/e169, https://doi.org/10.1212/nxg.0000000000000169. Accessed 13 Aug. 2023.
29. Rajagopalan, Sridharan, *et al.* "Single-Molecule Characterization of Oligomerization Kinetics and Equilibria of the Tumor Supressor P53." *Nucleic Acids Research*, vol. 39, no. 6, 18 Nov. 2010, pp. 2294–2303, academic.oup.com/nar/article/39/6/2294/2411764, https://doi.org/10.1093/nar/gkq800. Accessed 13 Aug. 2023.
30. Wei, Chia-Lin, *et al.* "A Global Map of P53 Transcription-Factor Binding Sites in the Human Genome." *Cell*, vol. 124, no. 1, 1 Jan. 2006, pp. 207–219, www.cell.com/cell/fulltext/S0092-8674(05)01399-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867405013991%3Fshowall%3Dtrue, https://doi.org/10.1016/j.cell.2005.10.043. Accessed 13 Aug. 2023.
31. Wade, Mark, *et al.* "MDM2, MDMX and P53 in Oncogenesis and Cancer Therapy." *Nature Reviews Cancer,* vol. 13, no. 2, 10 Jan. 2013, pp. 83–96, www.nature.com/articles/nrc3430, https://doi.org/10.1038/nrc3430. Accessed 13 Aug. 2023.
32. Kastenhuber, Edward R, and Scott W Lowe. "Putting P53 in Context." *Cell*, vol. 170, no. 6, 1 Sept. 2017, pp. 1062–1078, www.cell.com/cell/fulltext/S0092-8674(17)30953-4?_returnURL= https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867417309534%3Fshowall%3Dtrue, https://doi.org/10.1016/j.cell.2017.08.028. Accessed 13 Aug. 2023.
33. Weber, Genevieve L, *et al.* "Abrogation of PIK3CA or PIK3R1 Reduces Proliferation, Migration, and Invasion in Glioblastoma Multiforme Cells." *Oncotarget*, vol. 2, no. 11, 5 Nov. 2011, pp. 833–849, pubmed.ncbi.nlm.nih.gov/22064833/, https://doi. org/10.18632/oncotarget.346. Accessed 13 Aug. 2023.
34. Roel Verhaak, *et al.* "Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1." *Cancer Cell*, vol. 17, no. 1, 1 Jan. 2010, pp. 98–110, pubmed.ncbi.nlm.nih.gov/20129251/, https://doi.org/10.1016/j.ccr.2009.12.020. Accessed 13 Aug. 2023.
35. Kashyap, Anubha, *et al.* "The Human Lgl Polarity Gene, Hugl-2, Induces MET and Suppresses Snail Tumorigenesis." *Oncogene*, vol. 32, no. 11, 14 May 2012, pp. 1396–1407, pubmed.ncbi.nlm.nih.gov/22580609/, https://doi.org/10.1038/onc.2012.162. Accessed 13 Aug. 2023.
36. Freeman, Daniel J, *et al.* "PTEN Tumor Suppressor Regulates P53 Protein Levels and Activity through Phosphatase-Dependent and -Independent Mechanisms." *Cancer Cell*, vol. 3, no. 2, 1 Feb. 2003, pp. 117–130, pubmed.ncbi.nlm.nih.gov/12620407/, https://doi.org/10.1016/s1535-6108(03)00021-7. Accessed 13 Aug. 2023.
37. Hashemi, Mehrdad, *et al.* "Progress in Targeting PTEN/PI3K/Akt Axis in Glioblastoma Therapy: Revisiting Molecular Interactions." *Biomedicine & Pharmacotherapy*, vol. 158, 1 Feb. 2023, pp. 114204–114204, www.sciencedirect.com/science/article/pii/S0753332222015931#:~:text=Mutation%20or%20depletion%20of%20PTEN,in%20therapy%20resistance%20in%20GBM., https://doi.org/10.1016/j.biopha.2022.114204. Accessed 13 Aug. 2023.
38. Hu, Jiemiao, *et al.* "Regulation of Tumor Immune Suppression and Cancer Cell Survival by CXCL1/2 Elevation in Glioblastoma Multiforme." *Science Advances*, vol. 7, no. 5, 29 Jan. 2021, pubmed.ncbi.nlm.nih.gov/33571109/, https://doi.org/10.1126/sciadv.abc2511. Accessed 26 Aug. 2023.
39. Gomes, Sofia E, *et al.* "Convergence of MiR-143 Overexpression, Oxidative Stress and Cell Death in HCT116 Human Colon Cancer Cells." *PLOS ONE*, vol. 13, no. 1, 23 Jan. 2018, pp. e0191607–e0191607, pubmed.ncbi.nlm.nih.gov/29360852/, https://doi.org/10.1371/journal.pone.0191607. Accessed 26 Aug. 2023.
40. Gessner, Isabel, *et al.* "Selective Capture and Purification of MicroRNAs and Intracellular Proteins through Antisense-Vectorized Magnetic Nanobeads." *Scientific Reports*, vol. 9, no. 1, 14 Feb. 2019, pubmed.ncbi.nlm.nih.gov/30765836/, https://doi.org/10.1038/s41598-019-39575-7. Accessed 26 Aug. 2023.
41. Singh, Aishwarya, *et al.* "Advances in SiRNA Delivery in Cancer Therapy." *Artificial Cells Nanomedicine and Biotechnology,* vol.46, no. 2, 19 Apr. 2017, pp. 274–283, pubmed.ncbi.nlm.nih.gov/28423924/, https://doi.org/10.1080/21691401.2017.1307210. Accessed 26 Aug. 2023.
42. Wang, Jun, *et al.* "FRK Suppresses Human Glioma Growth by Inhibiting ITGB1/FAK Signaling." *Biochemical and Biophysical Research Communications*, vol. 517, no. 4, 1 Oct. 2019, pp. 588–595, pubmed.ncbi.nlm.nih.gov/31395336/, https://doi.org/10.1016/j.bbrc.2019.07.059. Accessed 26 Aug. 2023.
43. Siwen Hu-Lieskovan, *et al.* "Sequence-Specific Knockdown of EWS-FLI1 by Targeted, Nonviral Delivery of Small Interfering RNA Inhibits Tumor Growth in a Murine Model of Metastatic Ewing's Sarcoma." *Cancer Research*, vol. 65, no. 19, American Association for Cancer Research, Oct. 2005, pp. 8984–92, https://doi.org/10.1158/0008-5472.can-05-0565. Accessed 18 Feb. 2024.
44. W;Shi, Sun. "Advances in the Techniques and Methodologies of Cancer Gene Therapy." *Discovery Medicine*, vol. 27, no. 146, 2019, pubmed.ncbi.nlm.nih.gov/30721651/. Accessed 26 Aug. 2023.
45. Navarro-Marchal, Saúl A, *et al.* "Cancer Suicide Gene Therapy: A Patent Review." *Expert Opinion on Therapeutic Patents*, vol. 26, no. 9, 20 July 2016, pp. 1095–1104, pubmed.ncbi.nlm.nih.gov/27424657/, https://doi.org/10.1080/13543776.2016.1211640. Accessed 26 Aug. 2023.
46. Li, Man, *et al.* "Exploiting Tumor-Intrinsic Signals to Induce Mesenchymal Stem Cell-Mediated Suicide Gene Therapy to Fight Malignant Glioma." *Stem Cell Research & Therapy*, vol. 10, no. 1, 12 Mar. 2019, pubmed.ncbi.nlm.nih.gov/30867058/, https://doi.org/10.1186/s13287-019-1194-0. Accessed 26 Aug. 2023.
47. Westphal, Manfred, *et al.* "Adenovirus-Mediated Gene Therapy with Sitimagene Ceradenovec Followed by Intravenous Ganciclovir for Patients with Operable High-Grade Glioma (ASPECT): A Randomised, Open-Label, Phase 3 Trial." *Lancet Oncology*, vol. 14, no. 9, 1 Aug. 2013, pp. 823–833, pubmed.ncbi.nlm.nih.gov/23850491/, https://doi.org/10.1016/s1470-2045(13)70274-2. Accessed 26 Aug. 2023.
48. Michele De Palma, *et al.* "Microenvironmental Regulation of Tumour Angiogenesis." *Nature Reviews Cancer*, vol. 17, no. 8, 14 July 2017, pp. 457–474, pubmed.ncbi.nlm.nih.gov/28706266/, https://doi.org/10.1038/nrc.2017.51. Accessed 26 Aug. 2023.

DOI: 10.36838/v6i7.17

49. Somani, RR, and UV Bhanushali. "Targeting Angiogenesis for T reatment of Human Cancer." *Indian Journal of Pharmaceutical Scie nces*, vol. 75, no. 1, Medknow, Jan. 2013, pp. 3–0, https://doi.org/10 .4103/0250-474x.113529. Accessed 18 Feb. 2024.
50. Kloepper, Jonas, *et al*. "Ang-2/VEGF Bispecific Antibody Repro grams Macrophages and Resident Microglia to Anti-Tumor Phen otype and Prolongs Glioblastoma Survival." *Proceedings of the Nati onal Academy of Sciences of the United States of America*, vol. 113, no. 16, 4 Apr. 2016, pp. 4476–4481, pubmed.ncbi.nlm.nih.gov/27044 098/, https://doi.org/10.1073/pnas.1525360113. Accessed 26 Au g. 2023.
51. Aslan, Cynthia, *et al*. "Tumor-Derived Exosomes: Implication in Angiogenesis and Antiangiogenesis Cancer Therapy." *Journal of Cellular Physiology*, vol. 234, no. 10, 22 Feb. 2019, pp. 16885–1690 3, pubmed.ncbi.nlm.nih.gov/30793767/, https://doi.org/10.1002/ jcp.28374. Accessed 26 Aug. 2023.
52. Kore, Rajshekhar A, *et al.* "Hypoxia-Derived Exosomes Induce Putative Altered Pathways in Biosynthesis and Ion Regulatory C hannels in Glioblastoma Cells." *Biochemistry and Biophysics Report s*, vol. 14, 1 July 2018, pp. 104–113, pubmed.ncbi.nlm.nih.gov/298 72742/, https://doi.org/10.1016/j.bbrep.2018.03.008. Accessed 2 6 Aug. 2023.
53. D'Ippolito, Elvira, *et al*. "T Cell Engineering for Adoptive T Cell Therapy: Safety and Receptor Avidity." *Cancer Immunology, Immu notherapy*, vol. 68, no. 10, 21 Sept. 2019, pp. 1701–1712, pubmed. .ncbi.nlm.nih.gov/31542797/, https://doi.org/10.1007/s00262-0 19-02395-9. Accessed 26 Aug. 2023.
54. Banoun, Helene. "MRNA: Vaccine or Gene Therapy? The Safe ty Regulatory Issues." International Journal of Molecular Sciences , vol. 24, no. 13, *Multidisciplinary Digital Publishing Institute*, June 2023, pp. 10514–14, https://doi.org/10.3390/ijms241310514. Ac cessed 18 Feb. 2024.
55. Sun, Kai, *et al*. "Prognostic Value of DNA Repair Genes Based on Stratification of Glioblastomas." *Oncotarget*, vol. 8, no. 35, 27 Apr. 2017, pp. 58222–58230, pubmed.ncbi.nlm.nih.gov/2893855 0/, https://doi.org/10.18632/oncotarget.17452. Accessed 26 Aug. 2023.
56. Annovazzi, Laura, *et al*. "Chemotherapeutic Drugs: DNA Dama ge and Repair in Glioblastoma." *Cancers*, vol. 9, no. 6, 26 May 201 7, pp. 57–57, pubmed.ncbi.nlm.nih.gov/28587121/, https://doi.or g/10.3390/cancers9060057. Accessed 26 Aug. 2023.
57. Yeh, Charles D, *et a*l. "Advances in Genome Editing through Co ntrol of DNA Repair Pathways." *Nature Cell Biology*, vol. 21, no. 1 2, 1 Dec. 2019, pp. 1468–1478, pubmed.ncbi.nlm.nih.gov/317923 76/, https://doi.org/10.1038/s41556-019-0425-z. Accessed 26 A ug. 2023.
58. World. "Human Genome Editing." Who.int, World Health Org anization: *WHO*, 20 Oct. 2021, www.who.int/health-topics/huma n-genome-editing#tab=tab_1. Accessed 18 Feb. 2024.

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