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Genetic And Epigenetic Alterations In Glioblastoma

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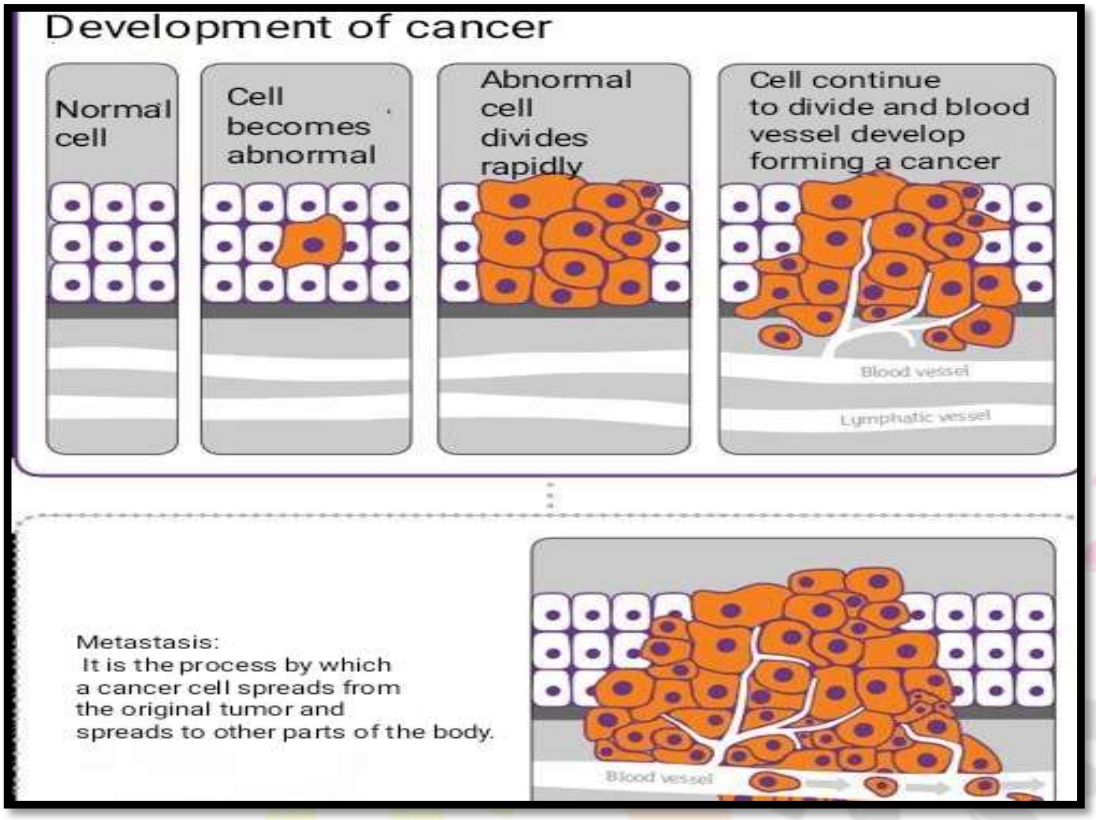
Abstract: Glioblastoma is the most common primary malignant brain tumor significant challenge due to its poor prognosis and limited treatment option. Tumor of the central nervous system (CNS) constitute approximately 2% of all malignancies. In these histone deacetylase inhibitor that emerged as epigenetic therapies for epigenetic change in GMB and helps tumor avoid immunological surveillance in molecular biology and genetics that have improved our understanding of GMB's understanding mechanisms ,molecular characteristics, clinical features, future direction here we systematically review of inflammatory associated epigenetic change and make treatment decisions in that Epigenetic terms including.

Keywords : Introduction of cancer, Glioblastoma, Epigenetic alteration, Mechanism and metabolism, Epigenetic therapies (diagnosis and treatment.)

Introduction:

cancer: It is type of disease in which abnormal cells growth out of control and spread to other areas of your bodies.



There are 200 types of cancer :some type of cancer are including following and other genetic types of Cancer are there

1] common type of cancer:

- **Carcinoma**: The most common type of cancer occur in human about 90%.
- **Sarcoma**: Theses type of cancer originate in connective tissues,bone and fat.
- **Lymphoma** : Theses type of cancer originated in lymphatic system.
- **Melanoma**:In these occurs in plasma cell.
- **Leukaemia**: cancer originated in bone marrow.[1]

2] Types of genetic cancer

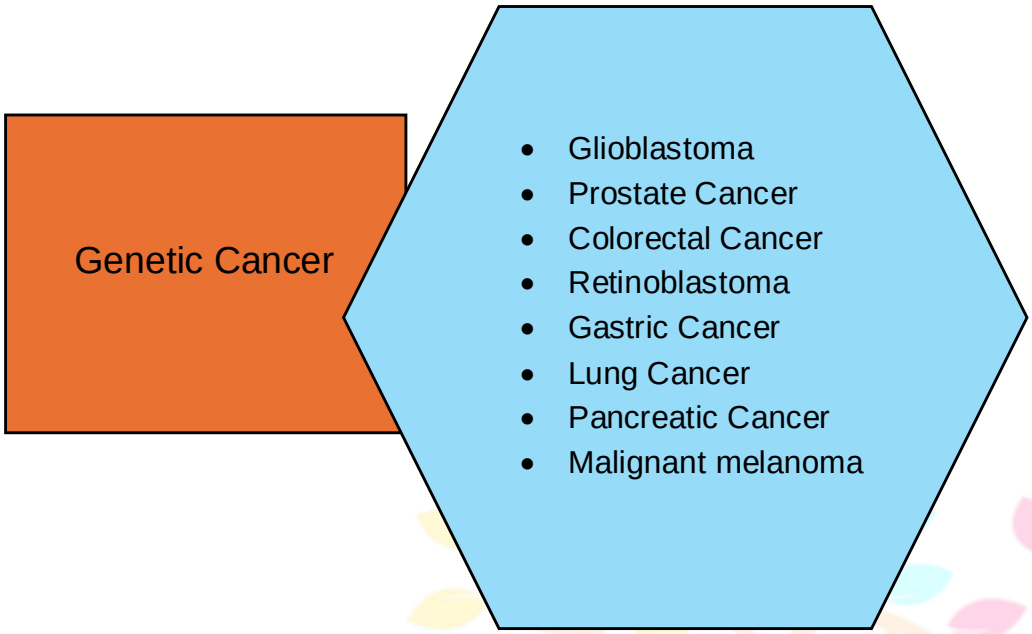


Fig: types of genetic cancer (2)

Glioblastoma: Gliomas and glioblastomas (GBM) are the most common and heterogeneous tumors affecting the brain parenchyma, accounting for 81% of central nervous system (CNS) tumors.[3]They may represent a tumor progression mechanism based on the selective maintenance of stochastically acquired favorable mutations at the level of genes involved in epigenetic processes.[4]It is the most common and deadliest type of primary brain tumor in adults. The annual incidence is estimated at about 3 cases per 100000 people.[3]GBM is a very heterogeneous disease. Tumor heterogeneity is reflected in histological patterns and epigenetic, genetic and transcriptomic changes.[5] Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant brain tumor.It diffusely infiltrates the surrounding brain and is characterized by a poor prognosis, with a five-year survival rate of 5.5% despite multimodal therapy [6]GBMs are classified into two main categories based on the presence or absence of specific genetic mutations. Primary (or de novo) GBMs occur without a progenitor Low-grade gliomas, while secondary GBMs develop from low-grade gliomas that progression to higher grade tumors.[7] Gliogenesis is the progression is caused by genetic and/or epigenetic changes that lead to abnormal gene expression, a process influenced by transcription factors (TFs), regulatory elements within DNA, chromatin insulators and chromatin-modifying enzymes [8]GBM patients were stratified into two categories based on GBM methylation status. The O-6-ethylguanine-DNA methyltransferase (MGMT) gene that repairs DNA damage Induced by TMZ and patients whose tumor contains methylated MGMT have a overall survival of 21.7 months compared to 12.7 months for those with unmethylated MGMT [9]Epigenetics is broadly defined as the study of heritable deviations in gene expression. Without any modification of the DNA sequence Also, the reversible nature of Epigenetic modification has sparked an effort to develop new therapeutic approaches More progressive measures aimed at combating GBM.[10,11]Current treatments for gliomas include surgery followed by radiation therapy and/or alkylating chemotherapy (eg, temozolomide). Recent studies have revealed underlying molecular genetic changes associated with glioma treatment, including the development of a hypermutation phenotype [12,13]Metabolism and epigenetics are important in regulation Tumorigenesis, stemness and malignancy, and are closely related in cancers.[14]DNA methylation and histone modification are the two classic types The most important epigenetic modifications. However, recently the role of non-coding RNAs, such as miRNAs, And its epigenetic modifications are on the way to discover more reliable and reliable prognostic and predictive biomarkers for GBM. [15]

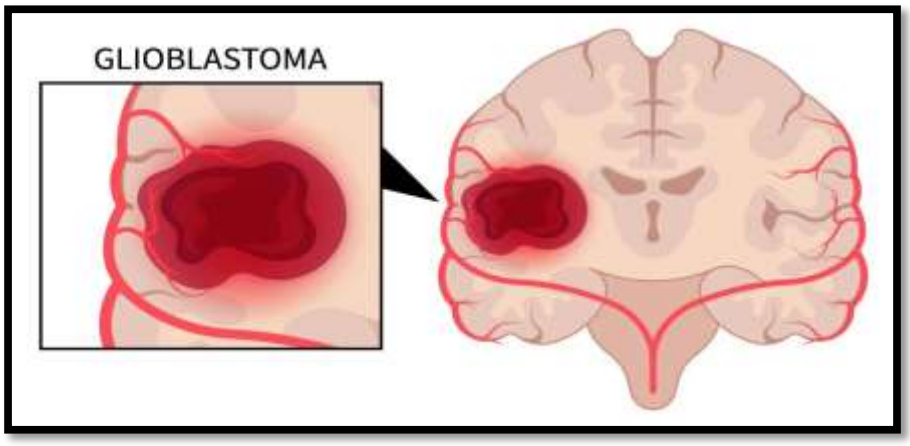


Fig Ref [16]

Epigenetic alteration in cancer: Epigenetic is formally defined as a Hereditary change in gene expression or Chromosomal stability with DNA methylation, Covalent modification of histones or non-covalent RNA Change in DNA sequence.[17]In these there are three types of epigenetic change are includingDNA methylation, histone modification, and noncoding RNA action.[18]

Genetic and epigenetic changes cause Disruption of cell signaling pathways in cancer Oncogenes can be up-regulated by Gain chromosomes, gene amplification, Translocations and activation of point mutations, And tumor suppressor genes may be inactivated From loss of entire chromosomes, large deletions, Intragenic deletions and point mutations. However, it is now clear that epigenetic silencing of Tumor suppressor genes, which can be considered functionally equivalent to mutations And eliminations, plays a major role in the development of cancer [19]DNA methylation patterns established during this period remain relatively stable in normal tissues. Methylation target molecules in mammalian DNA are the cytosine bases of CpG dinucleotides. In humans, 50–70% of all CpG sites are methylated [20-21]In somatic cells, DNA methylation patterns are usually transmitted to daughter cells with high fidelity. In general, this methylation occurs only on cytosines located between 5 and 039; guanosine in Cp dinucleotides of higher order eukaryotes.However, epigenetic DNA methylation varies Between normal cells and tumor cells in humans.[22]

Mechanisms and modifications of Epigenetic Alterations In Glioblastoma:

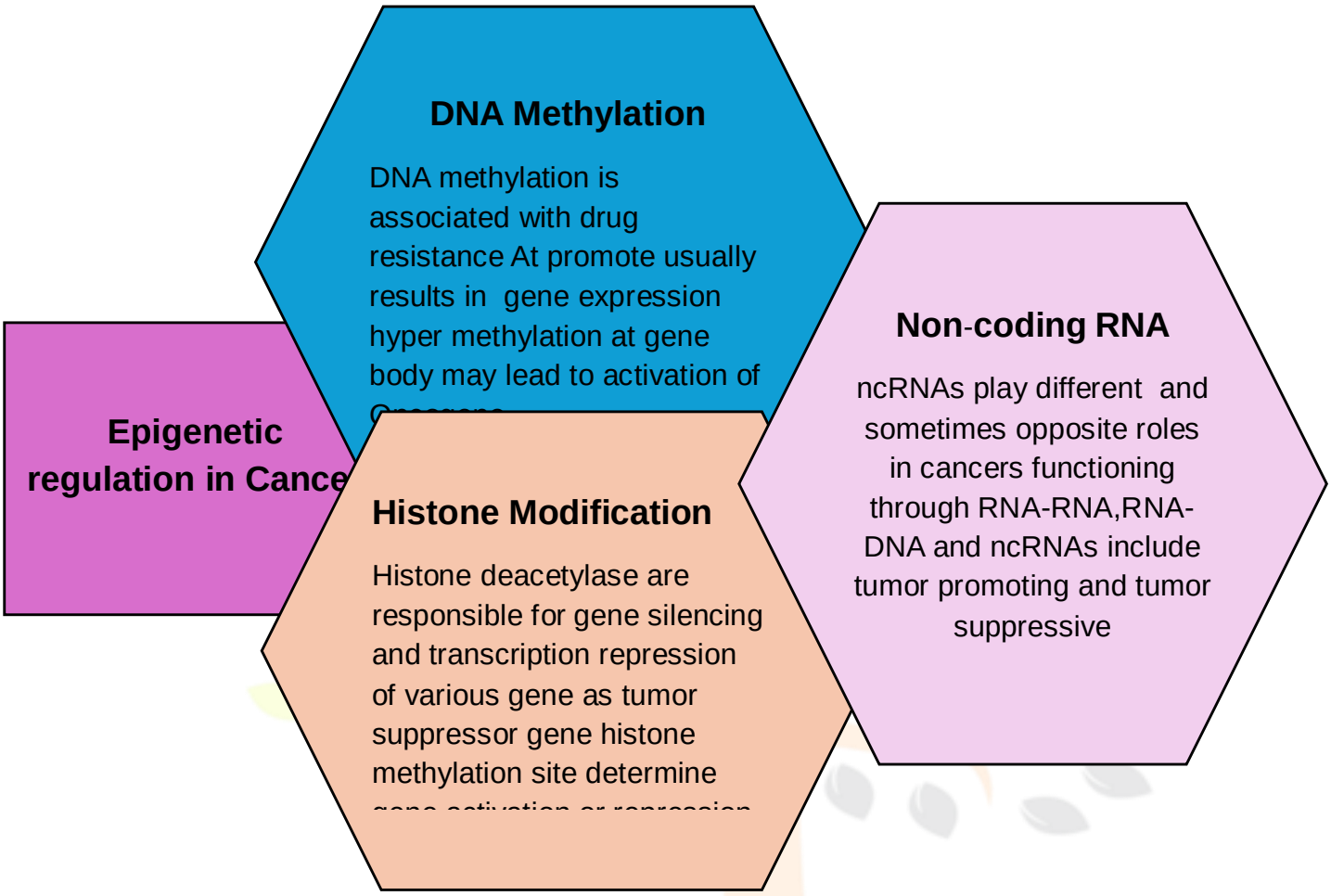


Fig: Epigenetic regulation [23]

In Glioblastoma Have Genetic Alteration In Several Type Of Gene Including:

- **Tumour Suppressor Gene:**

TP53(Protein p53):Changes in the TP53 gene are common mechanisms in a wide range Spectrum of human neoplasms. Spot changes of a copy of it Genes with loss of remaining wings are well documented in sub- Groups of several types of tumors, including colorectal carcinomas, breast cancer, liver tumors, lung cancer, and carcinomas of the head and neck. [24]Studies on human gliomas have shown that approx 25% of them have mutations in the TP53 gene Most of these Tumors are glioblastoma or anaplastic astrocytoma in adults, and Several low-grade astrocytomas and infantile gliomas were included. In the present study, we analyzed 120 gliomas in total Grades and histological types in 72 adults and 48 children for Mutations in the TP53 gene, accumulation of The TP53 protein to determine incidence and type of changes Of the TP53 gene are different between tumors of different histological types and between tumors in children and adults.[25]

PTEN(Phosphatase and tensin homolog):PTEN has been identified as a tumor suppressor gene, Encodes a dual-specificity phosphatase that dephosphorylates both residues eTyrosine phosphate and serine/threonine phosphate .The in vivo role of PTEN It appears that the dephosphorylation of phosphotidylino-Sitol 3,4,5-triphosphate.Mutations of the PTEN gene are present in about 30% of primary glioblastomas and are one of the most common genetic alterations in human cancers. Mutations in the PTEN gene reduce or eliminate the tumor suppressor function of the PTEN enzyme, which can lead to uncontrolled cell division and tumor growth.[26]

RB1(Retinoblastoma) :

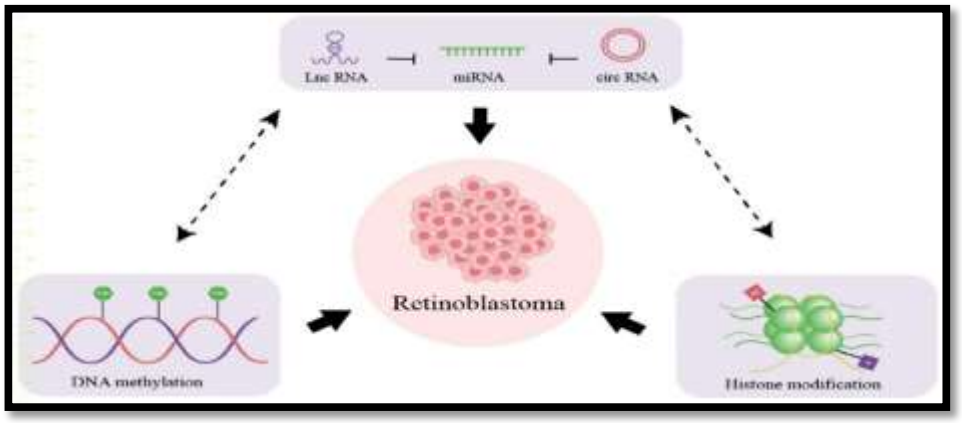


Fig-ref(27)

- **Type Of Oncogene:**

EGFR (epidermal growth factor receptor) : EGFR is a receptor tyrosine kinase They contribute to cell proliferation and differentiation associated with epidermal growth factor (EGF) and other growth factors Genomic alterations of EGFR result in signaling Independent of physiological ligands that promote pro-oncogenic processe (EGFR) gene is amplified in about 40% of glioblastomas (GBM). EGFR is the most amplified proto-oncogene in GBM. [28]

PDGFRA(platelet-derived growth factor receptor alpha): Alteration of PDGFRA is a marker of OPC-like cells, which are less differentiated and may show a high proliferative potential. Multiple GBM; however, these are limited to a few key genes, and only a few studies have used comprehensive gene panels.The proportion of glioblastomas (GBM) with amplification of the PDGFRA gene varies between studies, but is generally between 16% and 52.6%: [29]

IDH1/2(Isocitrate dehydrogenase):The gene isocitrate dehydrogenase 1 (IDH1), located at chromosomal locus 2q33. This mutation was present in 12% of GBMs and resulted in an Arg substitution in 90% of cases. IDH1 encodes cytosolic isocitrate dehydrogenase 1, Which is involved in the control of oxidative damage to cells Subsequent classification studies into groups of patients with Larger gliomas have been performed by our laboratory and others These studies showed that the IDH1 mutation is inversely associated with the grade of diffuse glial tumors, influencing71% grade II, 64% grade III and 6% primary glioblastomas. It is interesting to note that IDH1.[30-32]

- **DNA Repair Genetic:**

MGMT(O6-Methylguanine-DNA methyltransferase):O6-methylguanine DNA methyltransferase (MGMT) is a DNA repair protein encoded by the MGMT gene. Its promoter region consists of a cytosine-phosphate-guanine (CpG) island, which is a segment of DNA containing 98 CpG sites in a region that extends approximately 1.2 kilobases around the transcription start site .[33]

MLH1(MutL homolog1): In solid malignancies, where driver mutations involving methylation enzymes are rare, the ability of DAC to re-express genes that can decrease resistance to cytotoxic agents is of significant interest. Preclinical data showing several studies of the MMR protein mutL homolog 1 (MLH1) have identified aberrant hypermethylation in the MLH1 promoter in up to 15% of GBM samples.[34-38]

Therapies In Glioblastoma:

Targeted therapies of glioblastoma focus on specific molecular target to inhibit tumor growth and progression here some therapies:

Epigenetic Modifying Agents:

- DNA methyltransferases inhibitor
- Histone deacetylase inhibitor
- Histone methyltransferases inhibitor

Investigational Targeted Therapies:

- **Angiogenesis Inhibitor:**cilengitide,regorafenib
- **IDH1 Mutant Inhibitor:**ivosidenib,enasidenib
- **EGRR/EGFR Inhibitor:**gefitinib,afatinib

Immunotherapies:

- Checkpoint Inhibitor
- Cancer vaccine
- CAR-T therapy

Combination therapies:

- Chemoradiation+Epigenetic Modifying Agents
- Targeted therapy + immunotherapy (eg checkpoint inhibitors)
- Epigenetic Modifying Agents+Genetic Expression Modulator

Epigenetic Modifying Agents:

- **DNA methyltransferases inhibitor :**DNMTs are the main catalytic enzymes DNA methylation, mainly DNMT1, DNMT3A and DNMT3B. These three enzymes catalyze the formation of 5mC from Cysteines in CpG DNA islands and eventually removed Gene expression.[39]DNMTi constitute a class of analogues of Cytidines that are divided into two classifications; in one Class, a nucleotide analog binds to DNA to form a Covalent complex that promotes the degradation of DNMT.[40]DNA methyltransferase inhibitors Regulates tumor immunity The interaction of anticancer drugs with the host's immune system has been implicated in therapeutic response.The major histocompatibility complex (MHC) is in class I The core of antigen presentation and expression of MHC class I molecules in tumor cells is Often inhibited by irreversible mutations or reversible hypermethylations, which Results in a negative adjustment.[41]

Histone deacetylase inhibitor: Our understanding of the role of epigenetics in tumorigenesis and carcinogenesis has Has benefited greatly from the recent discovery of histone demethylases and their role in Regulation of post-translational modifications of chromatin, which can provide new Therapeutic tools to fight cancer. Effect of histone demethylases on lysine and arginine residues and their potential therapeutic value in targeting these enzymesThe use of histone demethylase inhibitors is a valuable adjunct to treatment Of cancer [42]

Histone methyltransferases inhibitor: Treatment-sensitizing effects in vitro and impairment of their tumor-initiating capacity in vivo Unfortunately, most glioblastoma cells are resistant to AR treatment due to defects in components of the AR signaling pathway and the reduced GSC reactivity. Members of the BMP (bone morphogenetic protein) family have been shown to inhibit GSC proliferation and induce GSC differentiation into astroglial and neuronal cells, thereby reducing the GSC population.[43-47]BIX01294, a specific inhibitor of G9a, induces autophagy or autophagy-associated cell death in several Tumor cell lines, but the underlying mechanisms have not been investigated in glioma cells. Dealing with BIX01294 reduced H3K9 and H3K27 methylation and, at higher concentrations, decreased the viability of mouse C6 glioma cells.[48]

Investigational Targeted Therapies:

Angiogenesis Inhibitor:(cilengitide,regorafenib):GBM is an extremely aggressive type of brain cancer. Antiangiogenic therapies, Which aims to disrupt the tumor's blood supply, have shown great potential as Therapeutic method for GBM [49]However, cancers gradually become resistant to it Anti-angiogenic agents.

With the most promising results, the following sections Will focus on data regarding its use in recurrent and newly diagnosed glioblastoma.[50]

IDH1 Mutant Inhibitor:(ivosidenib,enasidenib):Ivosidenib, a selective mutant IDH1 inhibitor, and enasidenib, a selective mutant IDH2 inhibitor, have shown clinical efficacy in patients. Ivosidenib, a selective mutant IDH1 inhibitor, and enasidenib, a selective mutant IDH2 inhibitor, have shown clinical efficacy in patients.[51]

EGRR/EGFR Inhibitor:(gefitinib,afatinib):Nimotuzumab is another anti-EGFR monoclonal antibody that binds more specifically to EGFR-overexpressing cells. It showed promising efficacy in a phase II trial in high-grade glioma, but failed to increase survival in a randomized phase III trial in patients with Dysfunctional WBC [52]. The heterogeneity of GB tumors, in which EGFR deletion and amplified EGFR mutations can coexist in different cells, leads to adverse effects resulting from collateral inhibitio of EGFR in normal tissues, as well as from redundant and alternative compensatory pathways [53]

Immunotherapies:

Checkpoint Inhibitor : Cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1), Also called checkpoints, are co-inhibitory receptors expressed on the surface of T lymphocytes To induce immunotolerance to self-antigens. WBCs (and other cancer cells) are overexpressed Programmed cell death ligand 1 (PD-L1) which, after interacting with PD-1, inhibits T-cell receptor (TCR)-dependent proliferation and IL-2 production and printing CD4+ and CD8+ response [54]. Thus, overexpression of PD-L1 causes the exhaustion of T cells and Leads to immunosuppressive TME that promotes the progression of GB and is associated withWorse patient outcomes [55]

Cancer vaccine : Early vaccines used dead or inactivated tumor cells, with very limited success. To improve efficacy, gene editing of tumor cells began in the late 1980s, including The expression of several immunostimulatory cytokines, granulocyte-macrophage colony stimulating factor (GM-CSF) is one of the most studied [56].

CAR-T therapy:CAR-T cells are genetically modified T cells (derived from autologous T cells). A patient's blood) that express an extracellular recognition domain of TSA (CAR, chimeric antigen receptor) and an intracellular activation domain to keep T cells constitutively active. The fusion between a CAR-T cell and a tumor cell induces a strong cytotoxic response Additional release of various proinflammatory cytokines that serve as protection against immunosuppressive TME [57]

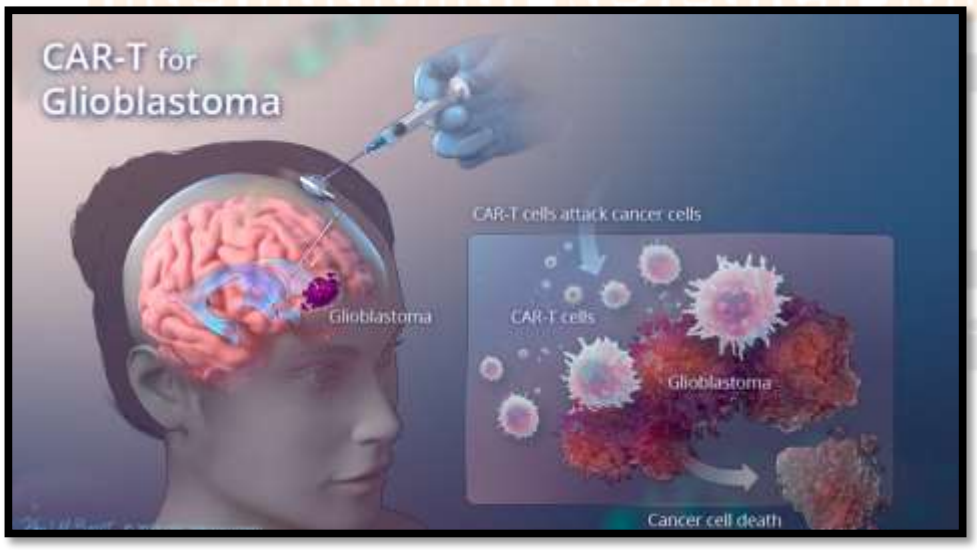


Fig Ref(58)

Combination therapies: Epigenetic modifying agents can be used in combination with chemoradiotherapy to treat glioblastoma (GBM) such as Histone Deacetylase Inhibitors (HDACI) Histone Deacetylase Inhibitors (HDACI).

- Chemoradiation+Epigenetic Modifying Agents
- Targeted therapy + immunotherapy (eg checkpoint inhibitors)
- Epigenetic Modifying Agents+Genetic Expression Modulator

Dignosis:

When seen on MRI, glioblastomas often appear as ring-like lesions. However, the appearance is not specific, as other lesions, such as abscesses, metastases, swollen multiple sclerosis, and other entities may have a similar appearance.Astrocytoma carries a mutation in IDH1 or IDH2, while this mutation is not present Glioblastoma. Thus, IDH1 and IDH2 mutations are a useful tool for differentiation Glioblastomas from astrocytomas, since they are histopathologically similar and differentiation without molecular biomarkers is unreliable. IDH wild-type glioblastomas usually have an expression Of OLIG2 lower than lower grade IDH mutant astrocytomas.[59]

Treatment:

- The brain is susceptible to damage from conventional therapies.

The brain has a limited ability to repair itself.

- Many drugs cannot cross the blood-brain barrier to act on the tumor.
- Treatment of primary brain tumors consists of palliative (symptomatic) care and therapies to improve survival.[60]

Some medications used to treat glioblastoma:

Histone deacetylase inhibitors (HDACi) HDACi are a well-studied class of epigenetic modifiers. O The pan-HDACi, Panobinostat, has shown promising results In preclinical evaluations for DIPG and is currently in trials A trial for children with DIPG . There Some concerns about Panobinostat's ability to pass BBB [61]

DNA methyltransferase inhibitors (DNMTi) – EZH2 Inhibitors : Treatment of PFA-CIMP+ cultures (positive phenotype for CpG island methylator) with DAC resulted in derepression of the complexes Genes containing EZH2 targets [62]

Bromodomain and extra terminal (BET) inhibitors:BET (bromodomain containing 2 and 4)protein can be Recruited by H3K27 acetylation and then cofactors are involved Transcriptional, but also activates RNA Pol II-dependent transcription [63]

Some other types of the drug used to treat glioblastoma :

CBP inhibitors :ICG-001, the structural inhibitor of CBP acetyltransferase, blocks the binding of CBP to other proteins. ICG-001 reduces cell survival, migration, invasion, and radio- Resistance in DIPG cells [64]

Conclusion:

Despite all the advances in medicine, the average survival of Patients with GBM did not improve significantly, perhaps because This tumor quickly becomes resistant to radiotherapy and chemotherapy. Epigenetic changes are a hallmark of GBM. The study of epigenetic markers and modifications of GBM provides valuable information about the molecular mechanisms underlying the disease. The meaning of these Epigenetic changes contribute to our understanding of GBM pathogenesis Contributing to tumorigenesis, progression and resistance to treatment, understanding these elements is essential for the development of effective modifications and therapies. Ongoing research aims to target epigenetic mechanisms, combine epigenetic therapies with existing treatments, and .identify new biomarkers

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