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Novel Biomarkers in Brain Tumor Diagnosis

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Abstract

The most frequent malignant primary intracranial tumors of the central nervous system are brain tumors. Frequently, they are discovered too late for effective treatment. For CNS malignancies, less invasive techniques are required for diagnostic and therapy response monitoring. Brain tumors cause the blood to contain molecular information. The use of liquid biopsies in place of tumor tissue is becoming more and more popular. These biopsies gather and examine tumor components found in bodily fluids. Tumor-derived extracellular vesicles, proteins, and nucleic acids can all aggregate in blood or cerebrospinal fluid and serve as biomarkers for tumors. Patients with glioblastoma have also had circulating tumor cells found in their blood in recent years. The authors of this literature review emphasize the importance, control, and frequency of molecular biomarkers including isocitrate dehydrogenase, O6-methylguanine-DNA methyltransferase, and epidermal growth factor receptor. On the other hand, during the last ten years, there has been a significant advancement in our knowledge of the early molecular processes in malignant primary brain tumors, and oncologists are now looking for novel Both the diagnosis and follow-up procedures make use of novel techniques for neuroradiological evaluation as well as medicines that specifically target these molecular events. This study focuses on the diagnosis and biomarkers of the most prevalent brain tumors.

Keywords: Biomarkers; Brain tumor; Isocitrate dehydrogenase; O6-methylguanine-DNA methyltransferase

Abbreviations: RT: Rhabdoid Tumor; AT: Atypical Teratoid Tumor; MGMT: Methylguanine-DNA Methyltransferase; PCR: Polymerase Chain Reaction; EGFR: Epidermal Growth Factor Receptor; EGFRvIII: EGFR Transcript variant III; RTK: Receptor Tyrosine Kinase; IDH: Isoketide Dehydrogenase; D-2HG: D-2-hydroxy-glutarate; a-KG: alpha-Ketoglutarate; ddPCR: droplet-type digital Polymerase Chain Reaction; GFAP: Glial Fibrillary Acidic Protein; TERT: Telomerase Reverse Transcriptase; LOH: Loss Of Heterozygosity; TIMP-3: Tissue Inhibitor of Metalloproteinases-3

Introduction

Brain cancer research has clearly captured the interest of many in recent years, including students, researchers, physicians, and even the public at large [1]. We now have a much better grasp of the physiological and pathological processes involved in brain cancer because to the development of bioinformatics, the integration of multi-omics data, and the rise of next- generation sequencing technology. Genes play a mostly dominant role in the complicated nature of cancer.

The use of outdated biomarkers and the length of time it takes to diagnose brain cancer are two of the disease's most striking features. Diet, lifestyle, medicine, and heredity are just a few of the environmental elements that cause these indicators to fluctuate dynamically throughout our lifetimes [2]. These changes have the potential to influence the brain's metabolic pathways by changing the make-up and function of noncancerous cells. The therapeutic potential of brain cancer is attracting increasing attention as a means to combat and cure a wide range of illnesses [3]. There is hope for reestablishing homeostasis and increasing host health through cancer- modulating strategies, such as dietary interventions, early detection, and therapy.

Moving beyond earlier purely descriptive studies with small sample populations, large-scale multi-geographic cohorts have also emerged, which is a major step forward. New correlations with a broad range of human disorders are being found on a regular basis in this respect. To meet this challenge, this Special Issue will provide a thorough overview of all the many parts of the latest research on brain cancer. In order to highlight its

significance in improving human health and avoiding disease, researchers tackled crucial and diverse themes linked to brain cancer in articles.

The initial research on brain cancer primarily emphasized the progress made in the clinical diagnosis and categorization of this disease. Immunohistochemical indicators have recently been introduced in the field of brain tumor diagnosis and prognosis [4]. Antibiotics are employed to specifically target the INI1/BAF47/SMARCB1/hSNF5 gene product for the purpose of diagnosing rhabdoid tumor (RT) and atypical teratoid tumor (AT) [5]. The absence or alteration of INI1, which is the genetic marker for RT and AT/RT, is demonstrated by the absence of the protein produced by this gene and the subsequent lack of immunological response [6]. Therefore, typical native cellular components that act as internal benchmarks, such as endothelial cells and reactive inflammatory cells, along with non-rhabdoid tumor imitators like medulloblastoma, display positive immune reactivity in their nuclear region. In contrast, the nuclei of RT and AT/RT tumor cells consistently show no immune reactivity.

An anti-INI1 diagnostic antibody test has been introduced, which serves as an immunohistochemistry substitute for confirming gene deletion/mutation by molecular testing [7]. The INI/BAF47 narrative exemplifies a model in which therapeutically meaningful findings derived from fundamental molecular biological and genomic research are eventually transformed into practical and widely available clinical laboratory assays [8]. Another set of clinically useful immunoreagents that have been recently introduced and deserve a quick mention are the novel proliferation markers, notably the immunostains for mitotic figures. Two These markers have the potential to significantly speed up the process of quantifying mitotic activity, whether by manual microscopic inspection or automated technology, in a more precise and unbiased manner. The potential clinical applications of mitotic figure immunostains extend beyond neuro-oncologic pathology and are likely to be of interest to all surgical pathologists who regularly encounter tumors where the level of cellular proliferation, especially the mitotic index, has been shown to have clinical diagnostic or prognostic significance [9].

In the field of CNS neoplasia, like in many other areas of surgical pathology, the influence of genetic and genomic methods on tumor diagnosis and classification is increasing [10]. Neuro-oncology examples include evaluating the deletion or mutation of the INI1 gene in RTs, silencing the gene O(6)-methyguanine-DNA methyltransferase (MGMT) in glioblastoma, and determining if oligodendroglial tumours have chromosomal deletions on 1p and 19q [11]. The G-CIMP phenotype seems to be more common in secondary GBMs than main ones, according to further research in low grade gliomas and GBMs. Low grade glioma patients that have a positive G-CIMP status are more likely to have an IDH1 mutation. In low grade glioma, G-CIMP remained a strong independent predictor of survival even after controlling for age and tumor grade [12]. Nevertheless, the latest evaluation of the TCGA data indicates that there is no survival advantage based on gene expression subtype class. However, G-CIMP positive patients with IDH1 mutations nevertheless have a better chance of surviving overall, as this study shows [13]. Keep in mind that this subset accounts for just around 10% of all GBM patients overall.

Biomarkers

While many cancer types may be distinguished from one another using molecular markers, only few offer consistent and accurate prognostic signs. We only include a few of the most well- known molecular indicators of brain tumors due to editorial restrictions. On chromosome 10q26 lies the gene that codes for O-6 methylguanine-DNA methyltransferase (MGMT) [14]. DNA repair is aided by O-6 methylguanine-DNA methyltransferase, which stops apoptosis by reversing DNA alkylation and eliminating the guanine-alkyl group. Different transcription factors, such as specificity protein 1 or nuclear factor kappa B, which activate the O-6 methylguanine-DNA methyltransferase promoter to drive the production of additional MGMT, greatly alter the expression of this protein [15]. About 40% of glioblastomas have MGMT promoter methylation. Since MGMT promoter methylation is only present in 36% of original tumors and significantly corresponds with the TP53 mutation (92%) in secondary GBM, it is more common (about 75%) in secondary glioblastoma. The expression of O-6 methylguanine-DNA methyltransferase has been linked to DNA-resistant alkylating drugs, including temozolomide, which is the main chemotherapy drug used to treat glioblastoma [16]. Reduced expression of this protein is associated with a marginally extended lifespan and reaction to temozolomide. Hegi et al. shown that in patients receiving TMZ, MGMT promoter methylation yields superior outcomes. In instances where methylation was present, the median overall survival was 18.2 months; in situations where methylation was absent, it was 12.2 months. The optimal TMZ treatment can be determined by assessing the methylation state of the MGMT promoter, as temozolomide is hazardous [17].

The most popular techniques for identifying methylation MGMT in glioblastoma patients are pyrosequencing, combinatorial PCR using MS technology, polymerase chain reaction (PCR), or SYBR Green [14].

Major signaling pathways and physiological responses, such as migration, proliferation, survival, and tumor development, are activated by the epidermal growth factor receptor (EGFR). One possible biomarker for glioblastoma is EGFR [18]. It is involved in growth factor signaling in healthy cells, but oncogenic alterations associated with cancer (variant expression, mutations) frequently result in ligand-independent oncogenic activity. About 40% of glioblastoma patients have elevated EGFR, which is frequently linked to high-grade malignancies. Tumors may include several dozen extra copies of EGFR. The EGFR gene encodes a tyrosine

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kinase receptor that is selective for particular growth factors. EGFR transcript variant III (EGFRvIII) is one of the most frequently researched EGFR mutations in brain tumors. It results from a histone alteration on the enhancer gene on chromosome 7p12 [14]. According to some research, the best predictor of a poor prognosis and low survival rate is overexpression of EGFRvIII in the presence of epidermal growth factor receptor amplification [19]. EGFRvIII may, however, be a good prognostic sign and indicate the long-term survival of patients with EGFRvIII who receive surgery, chemotherapy, or radiation therapy, according to other studies [20]. The response to receptor tyrosine kinase (RTK) inhibitors may also be predicted by this biological signature. RTK inhibition initially seems to help EGFR-amplified cancers, however results indicate that this medication is not always effective in treating them. Because EGFR mutation and amplification are prevalent in glioblastoma cells, they were designated as prognostic biomarkers. Owing to the tumor's proliferative nature, which is primarily regulated by important growth factors and their receptors, EGFR can activate processes required for the growth of cancerous GBM cells.

The primary job of the protein enzyme isoketide dehydrogenase (IDH), which is encoded by genes on chromosome 2. IDH is involved in the Krebs cycle's oxidative decarboxylation process. IDH has been divided into IDH 1 and IDH 2 courses. These isoenzymes reduce NADP + to NADPH while catalyzing the reversible oxidation of isocitrate to generate α-ketoglutarate. Cell- free defense against intracellular oxidative damage is offered by NADPH. The most prevalent mutation in IDH 1 or 2, which results in the oncometabolite D-2-hydroxy-glutarate (D-2HG) from alpha-ketoglutarate (a-KG), a normal product, is caused by a single-residue alteration that substitutes histidine for arginine [21]. It is still unknown how this promotes cancer, although it is most likely connected to how D-2-hydroxyglutarate affects DNA demethylases, which in turn increases methylation of DNA and histones. Additionally, D-2HG has been employed as a biomarker of therapeutic response. While isocitrate dehydrogenase mutations are uncommon in original GBM, they are prevalent in 73–85% of secondary GBM cases. IDH1-mutant cells are more radiosensitive than wild-type cells, and gliomas with a secondary IDH1 mutation exhibit enhanced chemosensitivity, as demonstrated by Tao et al. IDH mutations are therefore thought to be a favorable predictive indicator of survival for glioblastomas in stages II through IV. It is feasible to identify this biomarker by spectroscopy or immunohistochemistry. Determining the outcome of the IDH mutation in the tumor's development is the primary constraint on the use of this biomarker. Methods like droplet-type digital polymerase chain reaction (ddPCR) and pyrosequencing can also be used to identify mutations in isoform dehydrogenase.

The intermediate fiber protein known as glial fibrillary acidic protein (GFAP) is generated by astrocytes and other central nervous system cells. Compared to normal brain cells, it is found in tumor tissue at far greater concentrations. However, because of the so-called "sensitivity gap" caused by the heterogeneous/ low expression of GFAP on some tumors, which results in undetectable levels of GFAP released into the circulation, GFAP in the blood cannot be utilized as a particular diagnostic marker for a brain tumor. The degree of necrosis, intratumor GFAP expression, and tumor volume are all correlated with elevated blood concentrations of GFAP [22]. Additionally, the presence of isocitrate dehydrogenase mutations is linked to serum GFAP levels. Though heterogeneous, glial fibrillary acidic protein is now the most widely used marker for identifying circulating tumor cells, and its expression is often preserved in brain malignancies.

An enzyme of the ribonucleoproteinase family called telomerase reverse transcriptase (TERT) is involved in the replication of telomeres, which are repeating DNA sequences found at the end of chromosomes [16]. They eventually result in a permanent proliferative halt as they progressively shorten throughout subsequent cell divisions. Only expressed in stem cells, telomerase is the main enzyme that stops telomere shortening due to cell division. Additionally, throughout the development of cancer, it is essential for cell transformation and immortalization. It is suggested that two particular point mutations, C228T and C250T, in the telomerase promoter (pTERT), activate telomerase. These mutations have been observed in cancer cells. Brain tumors are among the malignancies where pTERT mutations have been discovered; normal cells have not shown these alterations. Elevated TERT gene protein levels are linked with pTERT mutations in a significant proportion of brain tumor samples. Owing to their frequent incidence, pTERT mutations found in liquid biopsies may be predictive of brain tumor prognoses and may aid in the development of future diagnostic procedures [23].

The loss of genetic material from one of the two alleles of a gene is known as loss of heterozygosity (LOH). Malignant neoplastic cells frequently include LOH, which primarily impacts tumor suppressor genes and reduces the body's ability to defend its systems against the development of tumors. In brain tumors, it is a frequent genetic occurrence [24]. Between 60 and 80 percent of primary and secondary brain cancers include LOH 10q. On chromosome 10, the three frequently deleted regions are 10q23–24 (PTEN), 10q14-p15, and 10q25-pter. The loss of the tumor suppressor gene PTEN, coupled with genes like MXI1, DMBT1, LGI1, FGFR2, and WDRI1, is the most significant of these three. One phosphatase that is crucial in blocking the PI3K/AKT/ mTOR pathway is the PTEN protein. Low-grade brain tumors that grow to high- grade glioblastomas are linked to PTEN mutations, loss of preferred tumor development, and deletion of the PTEN locus 10q25-pter. Brain cancers have also been linked to LOH on chromosome 22. Chromosome 22q is the most often lost gene; it is seen in 41% of primary tumors and 82% of secondary tumors [25]. The tumor suppressor gene TIMP-3, which codes for tissue inhibitor of metalloproteinases-3 (TIMP-3), is lost upon deletion

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of the 22q12.3 region. TIMP-3 triggers apoptosis and suppresses the development of tumor cells and the spread of cancer [26].

Numerous chromosomes, including 1p, 9p, 17p, and 19q, are impacted by LOH in brain tumors. Compared to primary brain tumors, secondary brain tumors are more frequently found to have chromosome 19q LOH. In primary brain tumors (12%) and secondary brain cancers (15%), loss of function (LOH) on chromosome 1 is an uncommon genetic event that is linked to prolonged survival. LOH analysis is carried out in patients with brain tumors by amplifying gene products using PCR and microsatellites. The well-known tumor suppressor protein p53 is encoded by the TP53 gene. p53 is regarded as the protector of the genome and has a number of roles in preventing the development of tumors. In contrast to main brain tumors, which only account for 30% of cases, TP53 point mutations were detected in secondary brain tumors 90% of the time, and in certain cases, in primary lesions at all [27]. One theory about how TP53 mutations contribute to the development of brain tumors is that they regulate the mevalonate (MVA) pathway. Using qRT-PCR techniques, it was established that the overexpression of MVA kinases and 3'-hydroxy-3'-methylglutaryl-coenzyme A reductase-two enzymes known to stimulate the growth of tumors-correlates with the activation of the MVA route and the TP53 mutation. In individuals with TP53 mutations, the use of mouse double minute 2 homolog inhibitors is effective [28].

New Therapeutic Approaches

Preclinical outcomes have been published by organizations for over a decade. A phase III study conducted in 2017 (CheckMate-143) compared anti-PD1 treatment with bevacizumab (anti- vascular drug), and nivolumab did not enhance overall survival [29] (Figure 1).

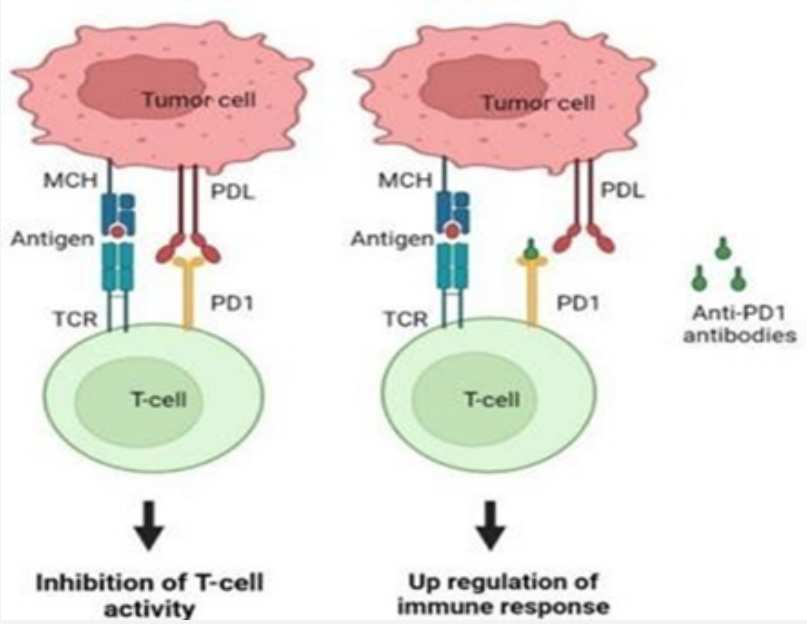

Figure 1: Anti-PD1 antibodies in T- cell activity.

VEGFA, or endothelial growth factor A, is used to treat recurrent glioblastoma. Phase III CheckMate-498 trial (NCT02617589) (US National Library of Medicine 2015) included patients with newly diagnosed O^6-methylguanine-DNA-methytransferase (MGMT) promoter- unmethylated glioma; the study's results were disappointing. In this trial, temozolomide (TMZ) with radiation was compared to conventional radiation plus nivolumab. In CheckMate-548 (NCT02667587 (US National Library of Medicine 2016a), a trial of patients with MGMT- methylated glioblastoma, nivolumab in conjunction with TMZ is being evaluated [30, 31]. The focus currently is on determining the etiological causes of therapeutic failures in order to eliminate barriers to successful immune checkpoint blockade. Immuno checkpoint therapy's moderate but notable effectiveness against other intracranial cancers, such as brain metastases of melanoma, may serve as a recent signal. Glioblastoma presents a distinct set of difficulties of its own. Two immune checkpoint blockade inhibitors that are linked to glioblastoma include low TMB and substantial intratumoral heterogeneity. Even within individual glioblastoma tumor cells, there are differences in the expression of oncogenic transcriptional programs, demonstrating the intratumoral heterogeneity that poses a unique challenge to immune targeting.

Looking Forward

Given the dynamic nature of high throughput "omics" technologies, we still have a long way to go before we can improve treatments and clinical outcomes for patients with brain tumors by integrating various kinds of high genome wide data.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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