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RECENT ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF GLIOBLASTOMA MULTIFORME

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ABSTRACT Glioblastoma multiforme (GBM) is the most dominant and most invasive glial tumors. The tumor occur in the glial cell in the brain or spinal cord, in which the patients have poor prognosis with five years chances of survival. GBM. Primary and secondary glioblastoma are the two types of the condition. The primary type accounts for 60% of the cases in adults above 50 years of age, it manifest without histopathological or clinical features, is from a less invasive precursor lesion, and symptoms have a short course of manifestation of about 3 months (Oh et al., 2017). The secondary type accounts for 40% of glial tumors, common in younger patient of below 45 years, and symptoms manifest in a relatively prolonged period of 1 to 10 years (Oh et al., 2017). However, the diagnosis and management of GBM was difficult when using traditional means, but advancement in diagnostic and treatment techniques for GBM hasten prognosis and improves the rates of survival. The following paper reveals the history of the diagnostic and management techniques used GBM detection and treatment with emphasis on the recent advancements used. Molecular analysis techniques of body fluids and biopsy form the advancements in diagnosis of GBM while new methods of treatment include nonmedicinal and computer model.

KEYWORDS :

Challenges in Traditional GBM Diagnosis

The location of GBM in the brain made it difficult to detect and treat using the traditional methods of diagnosis and management. The tumor occur in trans-barrier region in the blood-brain barrier (BBB) (Dréan et al., 2016). The composition of cells in the region creates a protective barrier that inhibit translocation of high –molecular weight substances and polarized material between the blood stream and the brain (Dréan et al., 2016). The conditions created by BBB means that without resection of the tumor, chemotherapeutic materials targeting the tumor cannot react it, which led to poor prognosis in traditional treatments. Besides, the traditional methods of tumor detection involved using medical imaging techniques that could detect the tumor at its advanced stages, which rendered interventions futile by 90% in which a patient had survival chance of 7 to 15 months (Ganipineni et al, 2018). Furthermore, the disturbance of BBB by the glial tumors cause low level detection of the tumor using of biomarker in peripheral blood tissues. Besides, the rapid growth of GBM in the BBB causes a hypoxic condition that triggers angiogenesis in the growth region, which creates blood supply to the tumor that nourishes it with oxygen and nutrients (Ganipineni et al, 2018). However, the formed vases during angiogenesis have abnormal structure such that they lack the intrinsic barrier function of a typical BBB. Noteworthy, all gliomas have a characteristic intact BBB region, especially on the edges if the tumor, which presents a major challenge on their response the chemotherapeutic treatments (Dréan et al., 2016). Hence, the GBM location in the BBB presents an adaptation trait that allow the tumor to form its blood supply and use the intact BBB on its periphery for protection against chemotherapeutic materials that makes treatment difficult.

GBM Detection Using Molecular Techniques

The most accepted GBM detection comes from the recent advancement of diagnosis using genetic tumor characterization techniques. The molecular genetic properties of gliomas in combination with their histological traits became the universal method of brain tumor classification since 2016. A pattern of DNA mutations and non-coding RNA deregulation is a common character in gliomas in which the frequencies of deregulation and mutations are different and relates with the specific brain tumor. Meanwhile, that application of genotyping on circulating tumor nucleic acid provides a new method of genetic mutation in glioma cells, which helps in classification, explains prognosis, and tumor burden. Moreover, the evaluation of circulation tumor nucleic acid helps in selecting and evaluating therapeutic efficacy window.

The analysis of genetic constituents of biopsy specimen obtained from patients with glioma is essential in the structuring of a distinguished diagnosis and determination the most suitable treatment option. Alternatively, circulating nucleic acid embedded in blood and other body fluids that are free or in association with extracellular vesicles are important biomarkers in early brain tumor detection and classification. Particularly, several genetic biomarkers of clinical significance are applied in routine diagnostic purposes. Of the many GBM genetic biomarkers that exist, ATRX loss, IDH1/2 mutation status, 1p/19q co-deletion, and MGMT promoter methylation remain the most used marker types (Silantyev et al., 2019; Gülten et al., 202). However, the widely adopted molecular techniques in analyzing the biomarkers that identify nucleic acid mutation are high resolution melting (HRM), droplet digital PCR (ddPCR), direct sequencing, and immunohistochemistry (Gülten et al., 202). Through these recent advanced GBM diagnostic techniques, oncologists can classify indistinguishable gliomas histologically using the absence/ presence of mutations in the circulating nucleic acids. Therefore, the detected mutation are vital in therapeutic choice, prognosis evaluation, and experimental values.

The challenges in analysis of genetic biomarkers used in detecting mutation in circulating nucleic acids in peripheral circulation resemble those encountered when deriving high-molecular polar compounds in the central nervous system. The systemic circulation has low compound concentration and abundance. Moreover, the molecules have low penetration ability in the BBB, which render it difficult to make diagnosis using derived nucleic molecules in the circulatory system. Some of the genetic molecules of importance in the molecular biology studies of GBM during diagnosis include small call of non-coding RNAs called micro-RNAs, small molecules, extracellular vesicles, circulating tumor cells (CTC), biological fluids, and tumor tissues.

miRNAs

miRNAs is a small class of non-coding RNAs (ncRNAs) that shows promising level of evidence in controlling various physiological and pathological pathways. In essence, miRNAs have short ncRNAs with 20-22 nucleotides in their chain that allow them to degrade corresponding mRNAs by hindering their pathway into a ribosomal machinery, which regulate the expression of specific genes (Regazzo et al., 2016). The new molecular techniques with a high throughput mechanisms offer large amounts of data related to miRNAs expression profiles in many cancers that have been generated. The innovative prediction tools applied in bioinformatics shows that a wide variety of miRNAs show modulation in many tumors that include gliomas. Moreover, many researchers have documented specific miRNAs related to diagnosis and prognosis of glioma and glioblastoma. For instance, a recent study certified a pane of five miRANs including miR-21, miR-648, miR-181d, miR-34a, and miR-125b that have specific involvement in TP53 and MGMT mutations; hence rendering them

mediators for glioblastoma development (Simion et al., 2020; Regazzo et al., 2016). Additionally, miR-181d and miR-21showed deregulation in other studies, which reveal their potential participation in glioblastoma carcinogenesis (Regazzo et al., 2016). Besides, miR-29a and miR-144 have strong association with glioblastoma development (Simion et al., 2020). The existing data on the use of miRNAs in GBM diagnosis and prognosis is vast but there is need for certification of the methods as a standard procedure in miRNAs diagnosis and prognosis.

Circulating Tumor Cells (CTC)

CTCs are isolated from and gets into the peripheral circulation of the primary tumor or metastasis. Circulating tumor cell detection approaches include using antibodies in immunohistochemical analysis and consequent genetic study, visual testing methods, and cell size evaluation (Chistiakov et al., 2018). The mechanism used by circulating tumor cells of glial cells origin is not completely known, but the glioma tumor is believed to be highly invasive. The cells infiltrate into the circulation, which enable them bypass the BBB or sometimes interrupt the BBB function during tumor growth (Chistiakov et al., 2018). The identification of tumor cells in peripheral blood samples from a patient has substantial therapeutic prospective in CNS malignant tumors, due to the benefit of diagnosing and predicting disease using blood samples without any intrusive and dangerous neurosurgical procedures. While GBM appears to be cranial-distinct tumor with distant migrations and invasions amounting to 0.5-2% of all GBM patients, many researcher have discovered several techniques including immunofluorescence-based cell selection, glial fibrillary acid protein-GFAP-based assay, and immunomagnetic to isolate CTCs from GBM cells, both in vivo and in vitro (van Schaijik et al., 2019). However further research is required in this area, since it is not yet apparent that CTCs are currently capable of explaining GBM activity, the incredibly low rate of metastases, or whether, at least for the majority, they are truly indicative of tumor genetic aberrations.

Extracellular Vesicles

Naturally occurring cell metabolites with a hydrophilic aqueous center enclosed in an external hydrophobic lipid bilayer is characteristic of an extracellular vesicles. The materials form a transport mechanism for lipids, proteins, genetic constituents, and many intracellular soluble components (Figueroa et al., 2020). The molecules regulate the microenvironment of cell homeostasis by controlling surrounding tissues and transmitting precise functional encryptions to the nearby cells (Yekula et al., 2019). By facilitating the transportation of distinct factors capable of controlling and deregulating multiplication, drug resistance, metastasis, angiogenesis initiation, and colonization (Yekula et al., 2019). Additionally, studies indicate that extracellular vesicles have close links to cancer progression. Glioma cells have shown to be capable of generating all forms of extracellular vesicles. For example, glioma cells secrete bioactive molecules, whose genetic constituents mirrors the parental cell characteristics, making extracellular vesicles a reliable diagnostic object for study. Glioma cells may create different extracellular vesicles types, including apoptotic bodies, exosomes, microvesicles, and oncosomes, an uncharacteristic large tumor type that produce vesicle cell selectively (Figueroa et al., 2020). Hence, detection of extracellular vesicle components in the peripheral circulation reduces the use invasive techniques when detecting glial tumors.

Advancement in the Treatment of GBM

The traditional methods of treating GBM included surgery, radiotherapy, and chemotherapy. The process involved starting with the surgical resection of the tumor to reduce its size and manipulate its blood supply. Thereafter, radiotherapy was applied to alter the oncogenes, which minimized the carcinogenic process and allowed chemotherapeutic material to reach the targeted tumor (Montemurro, 2020). However, the method had limited with survival rate of not more than 5 years. The tumor relapsed and became more aggressive, causing worse symptoms, poor prognosis, and death (Simion et al., 2020; Kuo et al., 2017). However, new methods applied in the treatment of GBM have advanced and they are giving better outcome in terms of delivery of chemotherapeutics beyond the BBB. The advanced methods include nanomedicine, and computational modeling.

Nanomedicine

In nanomedicine living organisms contain inherent nanoscale functional components, including proteins with a mean size of about 5 nm, and DNA molecules with a diameter of about 2.5 nm. To better explain the biological processes that exist at this nanoscale stage, nanotechnology techniques have evolved and the instruments form the basis of the field of nano-biotechnology, which combines biology, chemistry and physics (Kuo et al., 2017). Hence, nanomedicine is the use of nano-biotechnology in medicine, which is a subfield that has led to new directions in the growth, discovery, and delivery of drugs for the treatment of malignant brain tumors.

Drug administration to or inside CNS tissues poses major obstacles, including toxicity and crossing of BBBs. In brain cancer, the diverse tumor microenvironment, invasive tumor cells, and cancer-related changes in metabolism exacerbate these obstacles (Lynch et al., 20202). Nanomedicine provides a possible means of improving drug delivery to brain tumors by allowing improved permeability through BBB and precise targeting of subtypes of tumor cells by processes such as tumor stem cells and acidosis in the tumor microenvironment (Gao et al., 2016). The life-span of active drug compounds can be extended by nanoparticle-mediated delivery systems and provide for their regulated, continued and local release within brain tissue. It is essential to regulate the physiochemical properties of the delivery carriers, such as their size, overall surface charge, and chemical composition, to allow their efficacy (Lynch et al., 20202; Gao et al., 2016). Careful study to evaluate the cytotoxicity, biocompatibility and biodegradability of a nanoparticle is all important before clinical application. The life-span of active drug compounds is extendable by nanoparticle-mediated delivery systems and provide for their regulated, continued and local release within brain tissue. It is essential to regulate the physiochemical properties of the delivery carriers, such as their size, overall surface charge, and chemical composition, to allow their efficacy. A careful study to evaluate the cytotoxicity, biocompatibility and biodegradability of a nanoparticle is all important before clinical application (Lynch et al., 20202; Gao et al., 2016). To optimize the design of nanoparticles for the treatment of brain diseases, a thorough quantitative interpretation of how the physicochemical properties of nanomaterials influence therapeutic delivery and efficacy is essential. Computational modeling helps in meeting the need.

Computational Modelling

To reflect certain aspects of glioblastoma, several computational models have been developed, and the simulation tools developed can be used to predict tumor expansion and understand the unique microenvironment of the tumor. Overall, models can be categorized into various groups, ranging from minimalist models that only simulate tumor volume growth to molecularly complex models, including several genetic or proteomic processes involved in glioblastoma production and progression (Agosti et al., 2018; Ozdemir-Kaynak et al., 2018). Modeling methods have developed to provide insights into glioblastoma through various length scales (tissue, cell, and molecular) as researchers become more aware of the complexities of biology (Ozdemir-Kaynak et al., 2018). Thus the computer models are particular for genetic and protein analysis that helps in delivery of nonmedicines to the BBB.

Although the specifics and scope of the glioblastoma models are extremely complex, the common objective of all models is to accurately predict certain tumor progression features to control, avoid or reverse the invasive growth pattern of glioma. The more accurately this tumor growth is expected, the more reliable treatment for each cancer patient will be tailored. Three key glioma behaviors were concentrated in general models: vascularization, diffusion, and invasion potential (Agosti et al., 2018). The models consider key parameters such as hypoxia that strongly correlates with glioma invasiveness and malignancy; dynamics of immune response that can contribute to tumor regression and provide therapeutic benefits (Agosti et al., 2018). Diffusion in a three-dimensional space of therapeutic nano-particles reflecting the geometry and heterogeneity of the brain.

Computational modeling has the potential to provide predictive and explanatory frameworks that lack in vitro and in vivo models of glioblastoma for glioblastoma nanoparticle design and delivery (Ozdemir-Kaynak et al., 2018). Computational modeling is used explicitly to investigate the normal high heterogeneity of the microenvironment of the tumor and to compare the impact of manipulating molecular mechanisms in particular regions of the brain (Agosti et al., 2018). Furthermore, analysis of molecular signaling

pathways such as the one mentioned in the previous section can help to quantitatively show possible cancer targets, while mathematical models of mass transport phenomena allow projections of drug delivery to the brain and can assist in experiment design (Agosti et al., 2018). Furthermore, new researches that predict the progression of glioblastoma apply a number of exciting mathematical models (Ozdemir-Kaynak et al., 2018). Besides, an increasing number of studies focused on quantitative approaches to studying and enhancing the delivery of nanoparticles to the CNS across the BBB have been performed in conjunction with the rise in glioblastoma progression models. The effect on distribution across the BBB of nanoparticle formulation, shape, and binding properties has been previously studied both theoretically and in biological studies (Ozdemir-Kaynak et al., 2018). There are also a few studies that show alternative access across the epithelial blood, CSF barrier, to the CNS.

Anti-angiogenesis

Through its participation in many kinds of cellular processes, including endothelial induced mutations, and the development of a plasma membrane with new blood vessels, angiogenesis performs a significant role in the development of malignant gliomas. The process is regulated by vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), growth factor-beta transformation (TGF-β), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) (Wang et al., 2016). Besides, cancer cells metabolize endothelial pro-growth factors that combine VEGF with tumor angiogenesis, including simple FGF (bFGF). VEGF is secreted in hypoxia/necrotic areas by tumor cells and is expressed in a broad range of brain tumors (Winkler et al., 2018). VEGF binds to the VEGF receptor2 receptor. A number of studies strongly suggests that inhibition of VEGF and bFGF may be an important therapeutic strategy to substantially reduce angiogenesis (Winkler et al., 2018; Wang et al., 2016). Anti-angiogenic therapy thus presents a new possible cure for solid tumors.

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