REVIEW

Glia to glioma: A wrathful journey

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Abstract: Glial cells, unlike neurons in the brain, can undergo cellular division to maintain their functional continuity. However, sometimes this divisional attribute gets uncontrolled, which breaches tissue organization and transforms tissues into neoplasm. The proliferative abnormality of neuroglia results in one of the most dreaded neoplasm accounting for about 30% of all brain tumors—the glioma. The abnormal proliferation, high level of progression and invasive potential makes glioma one of the most lethal killers in its class. The pathological scenario becomes more moribund owing to poor prognosis and high mortality rate of the menace. Conventional onco-therapies yield dismal results compared to other soft tissue tumors. In time, with the advent of newer trends of prognosis and treatment modalities in the field of oncology, a hope for betterment is expected, but not yet achieved. These advancements would fetch some better results with proper and minute understanding of the biology of glioma, both at physiological as well as molecular level. In the present context, we have tried to document an insight to glioma biology that can serve as a primer to understand this lethal killer and its killing spree, with some approaches to combat its carnage.

Keywords: brain; glioma; neuroglia; astrocytoma; glioblastoma


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Introduction

Cancer refers to the abnormal cellular proliferation associated with changes in the plasticity of normal cells along with associated features such as escaping apoptosis, increased angiogenesis, metastasis, self-sustained metabolic growth signals incurrence, thwarting immune-surveillance and is caused by various carcinogenic hits primarily causing genomic aberrations[1–3]. However, the progression from a normal to neoplastic cell is somewhat treacherous. Various factors playing the role as the guardian of cell cycle process has to be defied for the initiation of cancer[4]. This breaching of normalcy is not an easy process and must undergo selective advantages[5]. Thus, cancer sometimes referred to as an “evolutionary disease” where the interplay between normal and altered cells within one’s own body results in a “touch-and-go” situation[6–8]. The hyper proliferation of glial cells and changing their plasticity and property within the Central Nervous System (CNS) and Peripheral Nervous System (PNS) are the etiological factors for the tumorous condition known as glioma. Although very fatal and claiming about 80% of all primary malignant brain tumors, the origin, pathophysiology and aggressiveness of glioma progression are not that much clear in nature[9]. On broad context, the conditions favoring the growth and progression of cancer cells can be interpolated with the Darwinian theory of evolution referring to microscopic selection and evolution[10]. This review work is intended to highlight some key aspects of glioma, its significant features, intricate nature, development and progression with reference to its abilities to cause mayhem in our nervous system, as well as the dearth of proper medical understanding and prognostic values that seems to intensify its gruesomeness.
A prologue to glial cells

For a comprehensive understanding of glioma, it is indispensable to have knowledge of neuroglia. Although it is easy to consider the brain as the hub of neurons for the processing of bio-signals, the fact is that almost half of the cellular volume in CNS, while catering to almost 85 billion neurons, contains neuroglia or glial cells with varied account of structural and functional entities \[11–13\]. Glial cells, as the term implies, “glues” the neurons to make delicate neuronal circuits. In the CNS, glial cells are of two distinct types: macroglial cells, comprising astrocytes (which function as the attachments to neuronal spatial distribution, provide nutrition to neurons from blood, and control the actions of neurotransmitters), oligodendrocytes (form myelin sheath and maintain neuronal terminals) and ependymal cells (line the internal fluid-filled cavities of the brain); and microglia or brain residential macrophage (which functions in immunological aspects, surveillance, and neural pruning) \[14–21\]. As depicted in Figure 1, glial cells and neurons work in a finely tuned manner with an indispensable correlation. Apart from these major glial cell types, there are some subdivisions of the major glial cells depending on their functions and locations. For example, astrocytes are of two types: fibrous (seen in white matter with thin and asymmetrical processes) and protoplasmic (seen mainly in grey matter with thick and asymmetrical processes) \[22,23\]. Ependymocytes, the chief constitute of ependymal cells, are seen mainly in choroid plexus and secrete CSF, whereas tanyocytes, another subtype of ependymal cells with long basal processes, line the floor of the fourth ventricle \[24,25\]. Like in the CNS, glial cells are also present in the PNS. The Schwann cells, which produce myelin sheath around neuronal axons, and the satellite cells, which covers the surface of nerve cell bodies, are two major representatives of glial cells of the PNS \[26,27\]. Less significantly, enteric glial cells, found in the digestive tract with PNS innervations, are thought to have a role in gastric motility and other gastro-homeostatic functions \[28\]. Apart from being structurally and functionally unique, these neuroglia are unique in their origin, too. Macrogial cells, such as astrocytes are derived from neuroepithelial progenitor cells, while microglial cells are thought to originate from yolk-sac-derived brain progenitor cells \[29,30\]. Schwann cells and satellite cells are derived from the

Figure 1. Functional correlations of glial cells in the CNS
neural crest[31,32].

Pathophysiological perspective on glioma

Glioma, principally the abnormal and uncontrolled cellular proliferation of neuroglia, is one of the primary and lethal neoplasms of the nervous system. Certain factors contribute to the lethality of this malady. Among the group of glial tumor, astrocytic tumors are one of the major contributors of the devastation, claiming a yearly incidence of 3%–5% per 100,000 people, with maximum prevalence in adults over the age of 45 years[33]. The generalized pathological symptoms of glioma include headache, vomiting, seizures, loss of consciousness, loss of memory, speech difficulties and visual blurring. Some of the initiating causes of glioma, although not properly understood, seem to have profound effect on tumor manifestation. Recently, an association of human cytomegalovirus (HCMv), first of the viral etiological factor associated with glioma, was pioneered and reported by Cobbs et al.[34,35]. Later, more evidences of this association made it clear that HCMV association interfered with the invasiveness and proliferative nature of glioma associated with the median patient survival[36–39]. Thus, HCMV can be of better prognostic aspect, as well as a novel glioma therapeutic target in treating glioma for increasing patient survival[40–42]. Moreover, HCMV gene expression has even been reported to be associated with glioma stem cell modulation by interfering with SOX2 and p-STAT3 that are responsible for stemness property of tumor cells[43]. Recently, RT-qPCR study in a Japanese population reported that, apart from HCMV, human papillomavirus (HPV) and human polyomavirus (HPyV) are also associated with the human glioma[44]. The effective number of ionizing radiations and even the increased use of mobile phones are nowadays considered to be the causative factors of glioma[45]. Surprisingly enough, cigarette smoking, unlike other types of events, does not play a significant role in glioma[46]. The most unique feature of glioma, unlike the other soft tissue tumor, is that glioma metastasis occurs only within the parts of CNS and its allied regions, although low amount of extra-neural metastasis (ENM) has also been reported in lungs, lymph nodes, bones and liver[33,47].

Glioma classification: A class apart

For a better understanding of glioma biology, a definite type of classification system depending on macro- and microscopic features has been developed. Among various types of classifications, such as the Kernohan system, the WHO grading system and the St. Anne/Mayo grading system, the classification of glial tumors by WHO has been regarded to be the most effective one[48]. Accordingly glial tumors, broadly characterized into neuroepithelial tumors, are further classified into two major types: primary glial tumors, which include astrocytoma (tumors of astrocytes with WHO grades I–IV), oligodendroglioma (tumors of oligodendrocytes with WHO grades I–III) and ependymoma (tumors of ependymal cells with WHO grades I–III); and accessory glial tumors, which include other neuroepithelial tumors such as angiogenic glioma and mixed neuronal-glial tumors with varied gradation by WHO grading system on the scale of I–IV, in which the grade I is benign and grade IV is the most malignant and invasive with high morbidity rate. Primary glial tumors, correlated with their identifying features and alterations of the respective candidate genes, are shown in Table 1.

Another subtle yet confusing classification arises depending on the age of onset of glioma: pediatric-type, comprising 0–19 years of age group as registered by Central Brain Tumor Registry of the United States (CBTRUS), and adult glioma in which the onset of the disease is above the age group of 20 years. Although, in some case such as glioblastoma multiforme (GBM), a WHO grade IV astrocytoma, the difference is clear between pediatric and adult depending on the gain of function of human chromosome 1q in adult and the loss of function of 10q in pediatric-type with a high amount of platelet-derived growth factor receptor-α (PDGF-α) expression[49].

Since 2007, the aforesaid classification orientation of human glioma, according to WHO, clearly relied on its histological understanding (described in Figure 2) along with its cellular and physiological interrelationship[50]. What is actually needed is the incorporation of advanced molecular and more genetic attributes in the course of glioma classification for better prognostic value. The ISN-Harleem 2014 Consortium entitled “WHO’s Next”, comprising 28 neuropathologists from 10 countries, focused on the questions of using non-histological criteria such as molecular diagnosis and advanced imaging properties to classify CNS tumors, including succeeding “layers” of tissue-based diagnosis information, histological classification, regular WHO grading and molecular interventions, along with separate tumor entity and
Table 1. Characteristic classification of primary glial tumors according to WHO and IARC 2007

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>WHO grade</th>
<th>Histological features</th>
<th>Genetical alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrocytic tumors:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subependymal giant cell</td>
<td>I</td>
<td>Increased large ganglioid astrocytes</td>
<td>No significant genetical changes</td>
</tr>
<tr>
<td>astrocytoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>I</td>
<td>Rosenthal fibres, microcystic nature, rich eosinophilic</td>
<td>Up-regulation genes such as SEMA5A, SCRG1, DPYSL3 linked to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>granules, highly vascular</td>
<td>neurogenesis</td>
</tr>
<tr>
<td>Pilomyxoid astrocytoma</td>
<td>II</td>
<td>Monomorphous piloid cells in a fibrillary texture, no Rosenthal</td>
<td>Altered TP53, mutation in IDH1/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fibres</td>
<td></td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>II</td>
<td>Microcystic tumor matrix, monotonous astrocytic morphology</td>
<td>TP53 mutation, upregulated PDGFR-α expression</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>II</td>
<td>Increased cellularity, nuclear atypia, increased</td>
<td>Altered ch.1q, gain of function of ch.1and 7, decreased MDM2</td>
</tr>
<tr>
<td>xanthoastrocytoma</td>
<td></td>
<td>vascularigenensis</td>
<td>level</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>III</td>
<td>Necrosis, nuclear atypia, increased mitotic activity,</td>
<td>EGF amplification and overexpression, p16 deletion, Rb1 alteration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pleomorphic cells, microvascular proliferation</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>IV</td>
<td>Increased multinucleated giant cells, mitotic atypia, high</td>
<td>Mutation of PTEN and TP53, no EGF expression, no p16 deletion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytoplasmic inclusion</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>II</td>
<td>Monomorphic increased oligodendroglial cells, specialized</td>
<td>LoH of ch.1p and 19q, MGMT promoter hypermethylation, loss of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>perinuclear “halo” pattern, nuclear atypia</td>
<td>function in Rb1</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>III</td>
<td>Microcalcification, prominent mitotic activity, cellular</td>
<td>LoH of ch.1p and 19q, MGMT promoter hypermethylation, PTEN</td>
</tr>
<tr>
<td>oligodendroglioma</td>
<td></td>
<td>pleomorphism and multinucleated giant cells</td>
<td>mutation, loss of ch.10</td>
</tr>
<tr>
<td><strong>Oligoastrocytic tumors</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>II</td>
<td>Necrosis absent, increased number of both astrocytes</td>
<td>LoH of ch.1p and 19q or TP53 mutation (vice versa), MGMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oligo-dendrocytes, microcalcification present</td>
<td>promoter hypermethylation, IDH1/2 mutation</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>III</td>
<td>Microvascular proliferation, high mitotic activity, atypia</td>
<td>LoH of ch.1p and 19q or TP53 mutation (vice versa), amplification</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of EGF, allelic loss of ch.10 and 11p</td>
</tr>
<tr>
<td><strong>Ependymal tumors:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subependymoma</td>
<td>I</td>
<td>Cluster of isomorphic nuclei in the enclosed fibrillary matrix,</td>
<td>No considerable aberration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>presence of small cysts</td>
<td></td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>I</td>
<td>Cuboidal or elongated cells enclosed in vascularized stromal</td>
<td>No considerable aberration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>structure</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>II</td>
<td>Monomorphic nuclear morphology, round to oval nuclei,</td>
<td>Aberration of ch.22, loss of ch.6q and 9q, MDM2 overexpression,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>perivascular pseudorosette and ependymal rosette</td>
<td>expression of IGF2, MMP12</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td>III</td>
<td>Increased cellularity, moderate mitotic activity,</td>
<td>Though largely unknown, loss of ch.9, 10q and 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>perivascular pseudorosette</td>
<td></td>
</tr>
</tbody>
</table>

Note: Excerpts are from the WHO classification of the tumors of the central nervous system, in association with International Agency for Research on Cancer (IARC) [48,53].

*Oligoastrocytoma has been dropped from the new 2016 classification scheme and was considered to be WHO grade II astrocytoma (IDH mutant/ATRX loss/1p–19q nondeletion) or WHO grade oligodendroglioma (IDH mutant/ATRX intact/1p–19q co-deletion) [53]. However, this chart is according to the 2007 scheme [48].

Differentiation between adult and pediatric types, where these clearly exists (Figure 3) [51,52]. This was reflected in the 2016 CNS WHO “update” (not a 5th edition) of the 2007 4th edition of the same, held in Dubai. Certain confusing glioma types with ambiguous histology, such as that of oligoastrocytoma, has been dropped from the new classification scheme and is considered to be WHO grade II astrocytoma (IDH mutant/ATRX loss/1p–19q non-deletion) or WHO grade oligodendroglioma (IDH mutant/ATRX intact/1p–19q co-deletion) [53].

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Figure 2. Hematoxylin–eosin staining of some paraffin embedded human glioma samples showing WHO classification along with histological specifications: (A) Astrocytoma II showing microcalcification and (B) hypercellularity with nuclear atypia (green arrow head); (C) Astrocytoma III with increased proliferation and (D) upregulated neovasculogenesis (green arrow head); (E) Astrocytoma IV or glioblastoma multiforme showing high deposition of necrotic tissue (stained as orange in hematoxylin–eosin) with outgrowth of vessels and (F) change in cellular plasticity (green arrow head); (G) Oligodendroglioma grade II having a hyperproliferative "sheet-like" hypercellularity with vascular sprouting (green arrow head), and (H) Myxopapillary ependymoma showing island-restricted microcalcification surrounded with dysregulated cell mass (green arrow head).

Figure 3. Brief outline of WHO 2016 classification of glioma

**Plasticity transformation: Oncocellular “stemness” multimodality**

Although it is clear from a cancer perspective that hyperproliferation associated with genetic and chromosomal alterations are the key ingredients for the transformation from glia to glioma, the advent of cutting-edge research has evoked some newer causes—one of them is “glioma cell stemness”. The lethality as well as therapeutic escaping nature of glioma, as reported similarly in some other types...
of cancer, are thought to be of equal importance due to the advent of this stemness property commonly referred to as glioma-initiating cell (GIC)\cite{54–56}. The sub-population of GIC, in its suggestive microenvironment, also seemed to be deeply associated with common neural stem cells (NSC) of CNS that possess the lifelong attribute to generate neural and glial cells at the sub-ventricular zone (SVZ), although a handful number of stem-like cells in the primary tumor can commence initiation in its multi-modal progress\cite{57–59}

From the various experimental outcomes and transcriptome analysis, it has been hypothesized that glioma might originate from the same neural stem or progenitor cells that normally differentiate or de-differentiate during neurogenesis. During the embryological state, the neurogenesis starts from two very unique regions of the brain, the sub-granular zone and the sub-ventricular zone, which harbor different niches of neural stem cells, and it gradually migrate through a very special event known as Rostral Migratory System\cite{60}. Gradually, successive interplay of differentiation and de-differentiation aid the transformation of radial astrocytic stem cells into neuron of hippocampal region via respective transformation to type 1 to type 2 to type 3 neural stem cells, while the ependymal cells lining the region of cerebrospinal fluid are under the crucial influence of various growth factors and their intricate signaling system such as Notch, Wnt, TGF-β, BMP, etc:\cite{61,62}. Periventricular adult NSC has been characterized to express a high level of GFAP-positive astrocytes, which along with combined loss of tumor suppressors p16 and p19 (causing increased expression of EGFR) and loss of p53 (causing over-expression of oncogenes such as c-myc) clearly indicate the de-differentiated property of astrocytes to give origin to GBM\cite{63–65}. Parallel to these modifications, the formation of type C progenitor cells from SVZ, which later become restricted to neuroblast and oligodendrocyte precursor cells (OPC), seem to inculcate a number of genetic alterations to manifest initial gliomagenesis\cite{66,67}

Moreover, high expression of PDGFRA-positive B-type cells in SVZ, mutational deletion of p53/Rb with alteration on RTK pathway, and even the modulation of NSC by cytomegalovirus tend to contribute greatly in gliomagenesis by affecting the stem cell hierarchy\cite{68–71}. Despite the immense connection between gliomagenesis-GIC-NSC, there are some other cell types such as NG2+ and the highly-proliferative OPC, scattered immensely in grey and white matter regions, that are expected to be more susceptible to pathways to gliomagenesis as glioma cells express high level of PDGFR and NG2, which are freely expressed in OPC\cite{72–74}

From post-natal period to the rest of the life, these NSC play a significant role in the formational processing of the neurons and neuroglia. Here, stresses such as cellular hypoxia, intrusion of oncogenic viral genomes such as cytomegalovirus, functional mutation of the isocitrate dehydrogenase 1 (IDH1) gene, loss of heterozygosity (LoH) of tumor suppressor genes by carcino-mitogenic hits etc., may result in the abnormality of the neural stem cell signaling system by altering the microenvironment that might drive cells into oncogenic activation, resulting in the formation of glioma stem cell (GTC) or brain tumor stem cell (BTSC) and more resistance to conventional chemotherapeutics such as Temozolomide (TMZ), and moreover tends to show typical hallmarks such as high level of angiogenesis and increased metastasis that renders the efficacy of glioma progression\cite{34,75}. Thus, the more stresses these glioma stem cells face, the more the tumor microenvironment and cellular niche would alter in favor of glioma progenitor cells, and the more severe they grow and invade (Figure 4). This makes the total resection of glioma through surgical procedures such as craniotomy almost impossible, with increased chance of recurrence and 14–15 months of post-operative survival in patients suffering from GBM\cite{62}.

A better understanding of the involvement of glioma-initiating stem cell population and subpopulation can bring out a radical targeted therapeutic approach for curbing this malady. GIC stays in a niche reported to be composed of stem cells, supportive cells, serum growth factors, immunological cells and ECM\cite{76,77}. The αV integrin, one of the key factors of ECM, seems to have a pivotal role in the increased pathological outcome of the GIC. Treatment with targeted αV integrin blocker RGD peptide such as Cilengitide seems to enhance the sensitivity of TMZ for inhibiting glioma progression and for better survival rate, and the result might come handy for better treatment of glioma\cite{78}.

**Cellular alterations: Epigenetic reprogramming**

Genetic up- and down-regulation, along with the activation and/or inactivation of various genes in the presence of carcinogenic stimulus, are well documented to be associated with the onset and devastation of human
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Glial cells are involved in the progression of glioma, which is supported by recent advancements indicating a very interesting involvement of epigenetic perspective that mostly includes DNA methylation, nucleosomal remodelling, histone modification and even interference by non-coding miRNA, which affects the spatial orientation of genomic packaging leading to varied entities of gene regulation without affecting the nucleotide sequences. DNA methylation pattern in glioma is considered to be one of the most profound epigenomical alterations that constitute hypermethylation-oriented down-regulation of genes related to tumor suppression (e.g. RB, p53, PTEN), suppressing of mitogenic cytokine signaling controllers (e.g. SOCS1, SOCS2) and silencing genes associated with DNA repair mechanism (e.g. MGMT). Interestingly, on the other hand, hypomethylation-oriented up-regulation of genes causing invasiveness (e.g. MMP9), disarray of chromatin packaging (e.g. DNMT3B) and increased glioma stemness (e.g. IGF2, IL-8) renders “epimutational” correlation with increased invasion, therapeutic escaping and abnormal proliferative nature of glioma.

Recent findings also suggest that epigenetic alterations are somehow linked to somatic gene abnormalities. Mutation in isocitrate dehydrogenase 1/2 (IDH1/2), one of the key cellular enzymes that facilitate the decarboxylation of isocitrate to 2α-ketoglutarate in normal cell, becomes altered by missense mutation at amino acid 132 in its active site, in which the arginine is replaced by histidine in glioma, resulting in the making of 2-hydroxygluturate (2-HG) oncometabolite in place of normal α-ketoglutarate (α-KG) that forms in oxidative decarboxylation process and interfering with the Jumonji class of demethylase and DNA hydroxylase which induces an array of changes including TET2 hydroxylase-oriented DNA hypermethylation, histone demethylase-oriented histone tail methylation, collagen propyl 4 hydroxylase-oriented collagen hydroxylation and HIF prolyl 4 hydroxylase-mediated hypoxia-induced factor that ultimately induces a high level of angiogenic expression of VEGF, making IDH1/2 one of the most prime markers in glioma with immense prognostic value. All of these phenomena cater to the initiation and perpetuity of glioma and also render problems in its treatment.

DNA methylation is a unique method in wild-type cells by which the addition of methyl groups in CpG island of DNA interfere with the binding of transcription factors and thus regulates the cell cycle. One of the key regulators of this process is O6-methylguanine methyl transferase.

Figure 4. Schematic representation of glioma progression with reference to glioma stem cell

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(MGMT) that removes the alkyl group from the O\(^+\) position of the guanine. In glioma, the abrupt expression of MGMT in high-grade glioma interferes with the medicine TMZ that induces the killing of tumor by alkylation in DNA, resulting in the least functional attribute of TMZ on high-grade glioma\(^{33,84}\). Thus, the expression of MGMT can surely be considered as a promising prognostic marker of glioma.

Newer trends suggest considering an effective expression level of microRNA (miRNA) as the prognostic approach towards glioma. miRNAs are small 12–27 bp-long stretches of ribonucleic acid that interfere with the regulation of transcription and post-transcription of gene. miR-21, one of the first reported microRNA, is believed to play a pivotal role in glioma progression, can be correlated with the grades of glioma in patients\(^{95}\). miR-21 has been reported to inhibit apoptosis in glioma by inhibiting factors such as PDCD4 and Cyclin D\(^{96}\). It also suppresses the anti-tumor effect of IFN-β\(^{97}\).

**Glioma progression: Cellular niche redefined**

In a disease such as glioma, much to utter dismay, the poor prognosis makes the disease an unbeatable winner thwarting all the medical support we implement. Most of the glioma in its growing phase remains undiagnosed and only come into monitor after the patients feel actual complications, although by that time the survivability of the patients has already been decreased by this con. One among many astonishing facts of glioma is that, unlike other organ-specific neoplasms, glioma not only escapes the immune system of the CNS but it also often manipulates the immunological cells in the course of its progression. Microglia or the brain macrophage might get influenced to secrete effective substances to reach to the glioma cell patch dissolving the ECM of the brain tissue through, but unwillingly they indirectly help glioma cells in their metastatic invasion through the damaged ECM done by themselves\(^{98}\). Indeed the presence and commemoration of brain macrophage or microglia (Figure 5) might lead to the better efficacy of glioma lethality\(^{99}\).

Glioma, like other tumors, effectively depends upon the gaseous exchange and the nutrition through blood. To increase in size and their invasiveness, glioma cells increase the sprouting of blood vessels by triggering the production of angiogenic cue Vascular Endothelial Growth Factor (VEGF), and thus the increased expression of the VEGF can be correlated with the increased gradation of glioma. For increased vasculogenesis, glioma cells are frequently found to be associated with the wall of blood capillaries and the approach of the tumor cells towards the endothelial cells undergoing effective chemotaxis, which is strongly induced by the peptide bradykinin that has been reported to function via B2 receptors abundantly found in glioma\(^{100}\). Upon binding of bradykinin, an influx of cellular Ca\(^2+\) helps the activation of matrix metalloproteinase 9 (MMP 9) by protein kinase C (PKC)-delta-mediated ERK/ELK1 pathway that destroys the ECM of endothelial cells, resulting in the metastasis of glioma cells\(^{101,102}\).

Glutamate, a neurotransmitter working via NMDA and GluR receptors in CNS, normally works at a very basic level as astrocytes in the synaptic cleft region quickly remove them by their unique Na\(^+\)-gated amino acid transporters known as EAAT1 and EAAT2, causing least glutamate reuptake. Contrary to this, the EAAT1 and EAAT2 receptors in the transformed cells are silenced, causing increased reuptake of glutamate. This phenomenon also induces high expression of cystine–glutamate antiporter (SXC) in glioma, which imports cystine in exchange for the highly available glutamate. This imported cystine is used to form a cellular antioxidant known as glutathione which decreases the chance of destruction of glioma cells due to intracellular molecular oxygens or reactive oxygen species (ROS) being an oxygen scavenger. Thus, the expression of SXC is highly upregulated in glioma during stress. So, it has been witnessed that in glioma patients, the expression of glutamate increases almost 100-fold, which can be a prognostic marker\(^{103}\). This apart, the increased amount of glutamate also results in seizures in glioma patients, better known as tumor-associated epilepsy\(^{104}\).

Thus far, the discussion related to glioma pathophysiology is a mere glance among many aspects of the abnormal changes in glioma microenvironment increasing the intricacy of this disease. With reinforcements ranging from the induction of hypoxia-inducible factors (HIFs)-related sprouting of vessels, merged with implemented paracrine factors such as CXCL12 in chemo- and radiosensitization by glioma cells, to the immune-modulation by chemo-attractants such as MCP-1 resulting in macrophage-oriented glioma growth and MMPs-mediated metastatic invasion, the alteration of tumor niche makes glioma readily aggressively as well as difficult to treat\(^{105–111}\).
Glioma: In search of epidemiology

To cope up with glioma, a cunning lethal destroyer on its own, with only some benevolent prognostic approaches will not be worthy enough unless and until proper epidemiological studies have been established. As the aptness of the term epidemiology depicts, a crucial monitoring system with a specific database and palliative patient care are the key approaches. Various countries have implemented tumor-dedicated databases to clearly look into the scenario. Database such as Central Brain Tumor Registry of the United States (CBTRUS) is one of the leading databases entirely dedicated to brain tumor. Epidemiological studies depending on the spatial distribution of tumor case histories with country, state, race, age, profession and sex variations have been monitored in these areas. Other databases such as American Brain Tumor Association and Cancer Research Foundation in UK also incorporate pathological aspects, archiving images, post-operative patient care and surveillance to battle better against glioma. However, sadly enough, third-world countries are still lagging far behind from establishing such a network. India, for example, which is the second most populated country in the world with an inbound of millions of tumor victims, is still to make any tumor database or registry network. For the last two decades in India, only two demo-epidemiological reviews have been published! The first one was the pioneering work depicting cross-sectional survey on intracranial malignancy in Kolkata and the suburbs in West Bengal in accordance with race-age-sex-profession, and the second review was conducted at Tata Memorial Hospital, Mumbai, on a given annual patient number of intra cranial malignancies. This scenario has to be changed for a better survivability against glioma.

Against the odds: Where do we stand and what is the future?

The old saying of “Prevention is better than cure” has the least to do when it comes to treating cancer and especially
in the case of glioma, as it seldom has a chance since one cannot prevent glioma whatsoever. So, if glioma is diagnosed either by conventional methods such as by doing a CT, MRI, fMRI, even PET or by the molecular expression analysis of newer prognostic markers, one has to undergo a regime of requisite treatment to maximize survival. The treatments can be categorized under some modalities. A very common practice is surgical resection such as craniotomy for the intracranial space occupying lesion (SOL). Depending on the place of occurrence of malignancy, craniotomy is one of the most favored surgeries, although in high-grade glioma, complete resection is almost impossible to accomplish and thus partial removal is done\textsuperscript{[118]}. Glioma, being an intracranial SOL, while progressing would push other cranial soft tissues together with the increased cranium pressure due to increased angiogenesis\textsuperscript{[119]}. So, the primary aim of surgery is to decrease the intracranial pressure in connivance with the administrative chemo-and radiotherapeutics, although number of complications arises in post-operative session including neurologic (aphasia, hemiparesis, etc.), regional (seizure, meningitis, etc.), systemic (sepsis, pulmonary embolism, psychosis, etc.) and above all, recurrence of tumor due to increased stress factor by surgery at a steady rate, which decreases survivability\textsuperscript{[120–122]}. In accordance with normal craniotomy, new surgical methods such as “awake brain surgery” which was performed at the John Hopkins Comprehensive Brain Tumor Center, USA, have also been implemented for avoiding surgery-oriented neurological and cognitive post-operative complications in patients where tumors are close to the visual or auditory cortex\textsuperscript{[123, 124]}. Surgery is done in an awakened (though locally anesthetized) condition amidst the procedure and alternatively putting to sleep at the beginning and the end of the procedure to minimize post-operative complications of important motor or speech perception in a real-time manner. At present, there are certain alternative translational treatment approaches that certainly have the effectiveness in treating glioma/glioblastoma. These processes include the incorporation of “biodegradable wafers” during post-surgical period in the malignant glioma resection to decrease the rate of tumor progression, increasing the overall patient’s survival; formulating “self-assembled amphiphilic nanocarrier peptides” for better delivery of drug to the zone of glioblastoma, effectively trespassing through highly selective blood–brain barrier; generation of heat, supplemented to surgical removal of SOL, at the site of glioma infestation by radiofrequency microwaves, lasers or magnetic force guided by stereotactic procedures (“onco-hyperthermia”) followed by scrupulous successive CT/MRI monitoring of patient, yielding gradual decrease in tumor mass increasing patients’ life span, especially in recurrent glioma; and the implementation of “tumor-treating field therapy” as a “non-invasive therapeutic approach” in combination with drugs such as Temozolomide using external anti-proliferative device, which is specially promising against recurrent GBM\textsuperscript{[125–128]}

However, surgical methods might not get that much chance to win unless it has been reinforced by successive radiation therapy and chemotherapy. Radiation therapies include Internal Radiation Therapy, in which liquid radioactive materials are pumped into the surgically removed portion of the tumor through a small catheter to stop further growth of the existing tumor cells; External Beam Radiation Therapy, where radioactive beams are passed penetrating the skull without any catheter to kill existing tumor cells left after surgery along with some normal tissue so that new cancerous transformation should be diminished; and Stereotactic Radio Surgery, where scrupulously guided radioactive beams are zapped exactly on the lesion site without harming the peripheral normal tissues\textsuperscript{[131, 132]}. A new variation of this last one is the Boron-Neutron Capture Therapy (BNCT) which has proven well-defined in treating glioma using the radioactive isotope of Boron\textsuperscript{[133–135]}. However, above all the labor it takes to apply, side effects such as hair loss, body weakness and mutation of non-malignant tissue by radioactive hits dwarf down the efficacy of these radiotherapeutic applications.

Chemo-therapeutics, on the other hand, also proved to be fruitful with representative components such as Temozolomide, which induce the addition of alkyl group in the tumor cell DNA and interfere with its replication cycle; Procarbazine, which yields hydrogen peroxide to form molecular oxygen that can break hydrogen bonds of DNA (with side effects such as numbness, intense pain, inhibition of liver CYTP450 oxidase); Lomustine, which also damage tumor cells by alkylation and it is extremely lipid-soluble drug that can easily diffuse through the blood–brain barrier; and Vincristine, a tubulin inhibitor that arrest mitosis in metaphase (with side effects such as neuropathy, constipation and hairloss\textsuperscript{[136–139]} Sometimes Procarbazine–Lomustine–Vincristine trio are used in a combination medically termed as PCV to treat glioma\textsuperscript{[140]}. Although seem to have a significant role in arresting glioma,
characteristic side effects of these chemotherapeutic agents cannot but dim their potentiality. Moreover, resistance and resurgence of glioma even after successful completion of drug regime is one of the vital aspects to magnify the dismal situation\(^{[141]}\). Of course, continuous research in the field of cancer therapeutics have now a days yield many beneficial results. Various prognostic views have been stressed on the properly guided therapy with subsequent delivery systems. Patients with high-grade glioma and having low sensitivity to TMZ due to increased expression of MGMT are administered with a combination of TMZ and radiotherapy\(^{[142]}\). Anti-angiogenic drug trials such as Bevacizumab (also known as Avastin) specifically interacts with VEGF receptors and inhibit glioma angiogenesis, although anti-angiogenic medications are extremely restricted as glioma uses other factors such as PI3K, HIF1-α, MMPs for sprouting blood vessels apart from VEGF\(^{[143]}\). A new kind of glioma treatment, popularly known as “case by case” treatment is where glioma-associated secondary disease such as neurofibromatosis type 1 (associated with astrocytoma) and tuberous sclerosis (associated with giant cell glioblastoma) are treated in context to the primary glioma lesion to soothe patients at to greater extent\(^{[144,145]}\).

Last but not the least of another promising inventory in the fight against glioma is the immunotherapeutic approach through designing glioma vaccines. Novel but effective as the concept is, it depends on factors such as the choice of proper antigenic targets, good delivery system, effective antigen-presenting property and least side effects. Targeted immuno-therapeutic with combinational adjuvant therapies are showing a picture of prominence in this regard\(^{[146]}\). Certain novel immunoproteins are also reported to perform in glioma treatment. T11 target structure (T11TS), one of the most promising immuno-therapeutic glycoprotein isolated from the membrane of sheep erythrocyte, has been found to either induce Bax–Bid–mitochondrial cytochrome c-mediated caspase-related glioma cell destruction or inhibit VEGF-mediated angiogenesis by decreasing the expression of PI3K-Akt, which comes handy in glioma treatment, though it is still awaiting clinical trial\(^{[147–149]}\).

Joining all these criteria, vaccine trials have been made against glioblastoma with its antigenic targets such as epidermal growth factor receptor variant 3 (EGFRvIII), glioblastoma stem cells or oncoproteins of cytomegalo virus and are achieved through the procurement of tumor lysate from resected GBM or through the synthetically formed protein cocktail of effective oncoproteins\(^{[150–153]}\). Some great review works by Oh et al. and Xu et al. are quite capable to avail information on glioblastoma vaccine trials\(^{[154,155]}\). Newer trends in composite state-of-the-art treatment trials are also proving to be helpful in the fight against glioma. The high number of Na+-pumps in glioma cell, which are responsible for its high-end growth and invasion, can be targeted selectively by certain novel components such as Cardenolide to curb down the menace\(^{[156]}\). The increased activation of Rictor-mediated mTORC2 in glioma cell for the hike in its progression has been reported to be inhibited by miRNA-153, which can be a potent choice of future molecular therapeutic choice against the battle with glioma\(^{[157]}\).

A number of future trials against glioma has been furnished by Farrimon, which range from injecting thermal nanoparticles at tumor site with gradual teasing generating heat and burning the tumor from within, to using anti-cancer hat that creates electromagnetic pulse and interferes with cancer cell proliferation, to undergo anti-angiogenic gene therapy such as VB-111 that targets the angiogenic notion in glioma\(^{[158]}\).

**Conclusion—with heartfelt hope**

The nature and manifestation of glioma, as we have highlighted in the preceding sections thus far cannot but ironically indicate towards the distorted poetic notion, *If glioma comes, can death be far behind!* Shattering, but true indeed. Regardless of all efforts the scientific communities and medical practitioners have made so far, they are befooled time and again by a mere clump of tiny cells with a shady *de novo* ancestry. Death might be inevitable but chances are there for betterment. A comprehensive and proper understanding of each and every futile move that glioma makes might get handy in advancing us one step further. An establishment of nation-wide and world-wide cancer registry might play a handy knock to understand and deal with the problem better. Physico-medical as well as psychological aspects of treatment might give patients some more precious time to live on this beautiful earth. Glioma, one of the most ruthless and obnoxious maladies of our brain, can only be out-witted by in-depth research and analysis of the mysterious abyss of an ever-craved structure at the dome of our body we call the brain.

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