ADVANCES IN BRAIN TUMOR THERAPY: ROLE OF THE TUMOR MICROENVIRONMENT IN PHARMACOLOGICAL STRATEGIES

Navdeep Singh*, Priyanka Chhabra, Tawqeer Shafi
School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab, India

ABSTRACT

Glioblastoma and other high-grade gliomas (malignancies) remain among the most clinically recalcitrant cancer subtypes due to rapid response phenotype, the general insensitivity to conventional therapy and complex tumor microenvironment (TME). The mutual interaction between the tumor cell and the surrounding micro-environment synergistically promotes the survival of cancer cells and their invasion, on the one hand, and acts as effective obstacles to the application of pharmacological methods, on the other hand.The current review overviews the recent progress in cancer treatment in the brain including the pharmacological approaches to TME elements. Recent antineoplastic anti-angiogenic drugs, the first immunotherapies with the use of immune checkpoint blockers and CAR-T cell therapy, and the combination of antineoplastic agents with modulations of metabolism, stroma, and TME (extracellular matrix) are evaluated against recently conducted clinical trials and supporting preclinical studies. At the same time, advancements aimed at overcoming the challenges associated with the blood brain barrier such as nanoparticle based and biologic based are touched upon. New modalities of therapy such as nanoparticles, biologics, and gene editors are noted to have the potential of redefining therapeutics.Nonetheless, despite the great achievement that has been achieved, there are major challenges that still exist including tumor and TME heterogeneity, ineffective preclinical models, and adaptive resistance management.The review highlights the significance of incorporating personalized medicine models and combination approaches towards optimizing therapeutic outcomes and reducing unwanted effects.In summary, addressing the brain tumor microenvironment is a worthwhile enchantment that has the prospect of creating a vital enhancement in patient outcomes. Intensified multidisciplinary research and well-conducted clinical trials would be essential in realizing the transformation of the breakthroughs into long-term and practical contributions to value-adding initiatives to the patients with brain tumors.

Keywords: Brain Tumor Microenvironment, Glioblastoma Therapy, Tumor Angiogenesis, Immunotherapy in Brain Tumors, Blood–Brain Barrier Drug Delivery, Tumor Resistance Mechanisms.

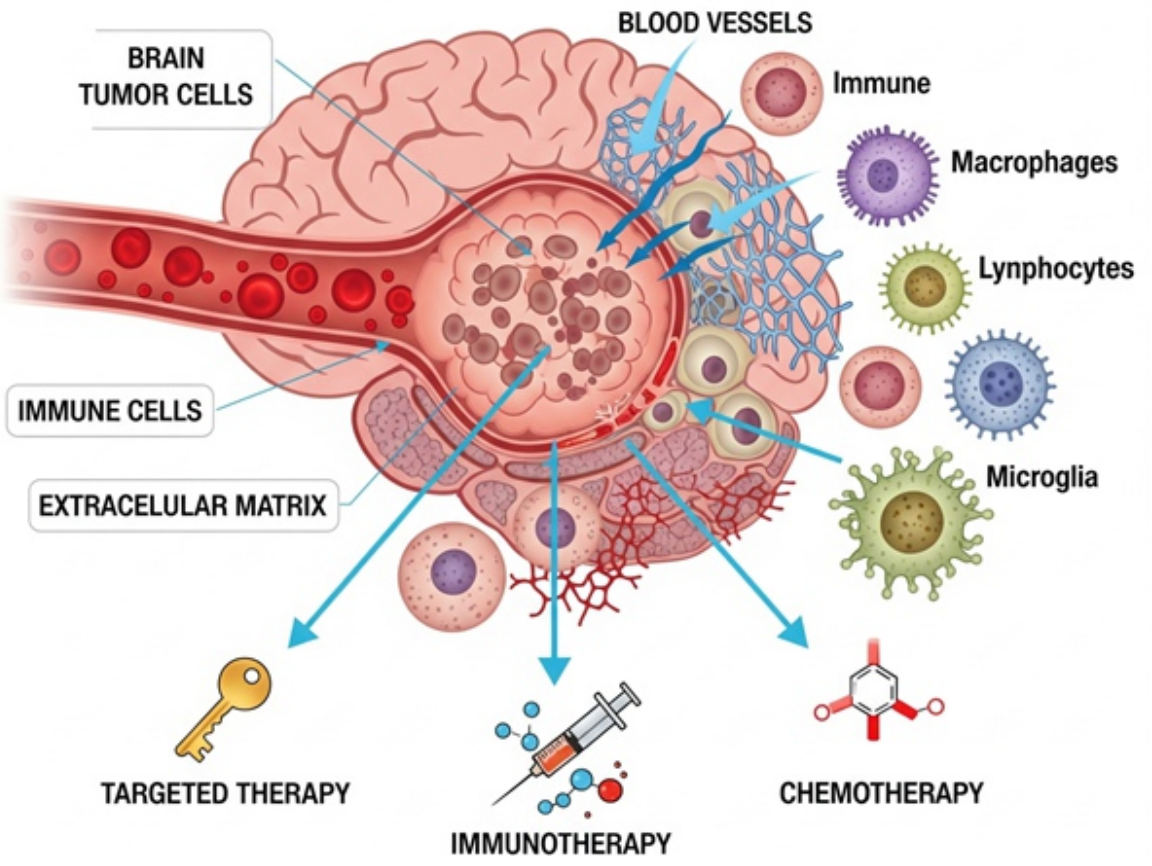

Figure : Pharmacological Strategies Leveraging the Brain Tumor Microenvironment

This graphical abstract is called Advances in Brain Tumor Therapy: Role of the Tumor Microenvironment in Pharmacological Strategies. The graphical abstract shows how brain tumor cells and the microenvironment (TME) around them are closely related. It emphasizes the different elements of TME including immune cells (macrophages, lymphocytes, microglia) and blood vessels and how the arising pharmacological approaches, such as targeted therapy, immunotherapy, and chemotherapy, are to communicate and take advantage of these factors to enhance the management of brain tumor.

INTRODUCTION

Brain tumors are heterogeneous, very challenging class of central nervous system tumors, which impact patients of all ages, yet have devastating implications when the disease involves adults under high-grade glioma or children confronted with embryonal or medulloblastoma type neoplasms [1, 2]. Epidemiologically, although primary brain tumors make up less than 2 percent of all cancer reported around the globe, the rate of incidences is increasing and the recent statistics of cancers on a global scale show over 300,000 new cases expected to be recorded each year[3, 4]. These tumors have a disproportionately negative clinical significance in relation to their incidence, and they are fraught with significant morbidity, cognitive decline and high mortality rates especially in those involving eloquent or deep seated areas of the brain[5, 6]. Glioblastoma, the most malignant of the primary brain tumors of adult patients, has been infamous in that it has a median survival of only 1520 months after aggressive multimodal treatment[7]. Conventional treatment modalities such as maximum safe surgical resection, external beam radiations and chemotherapy option like temozolomide tend to have a temporary control effect with majority of them developing progressive disease and ultimately developing the recurrence [8]. The examination of disease and outlook are further confused by the unique biological and molecular heterogeneity among various subsets of brain tumors and are necessitated to be replicated by the design of disease-specific interventions[9].

The modern scientific terminology has moved more and more to the issue of the complex dynamic environment of the tumor (TME), which goes beyond the paradigm of a malignant cell[10]. Today, the TME is the research focus due to its complexity as an ecosystem system, including cancer-associated fibroblasts, tumor-associated macrophages and microglia, pericytes, neural stem-like cells, endothelial cells, and the organized extracellular matrix[11]. This complex environment does not just facilitate or favor the proliferation of tumor cells, angiogenesis, metabolic reprogramming, and immune escape, but it also physically and functionally hinders efficient delivery of drugs through the reinforcement of blood brain barrier and suppression of immune system[12]. A strong preclinical and clinical evidence demonstrated TME components as one of the drivers of intrinsic and acquired resistance, proving the insufficiency of monotherapies targeting only the tumor cells[13]. Such a review, then, is both an attempt to synthesize the emerging knowledge about TME biology, as well as critically evaluate emerging pharmacological approaches that seek to exploit or interfere with TME interactions, and into the understanding of novel approaches, including immunomodulation, anti-angiogenesis, and novel drug delivery vehicles which may ultimately translate to better survival and quality of life of patients[14]. When describing these developments, we also mention the persisting issues and the vision of this multidisciplinary fight with the aim to outrun this deadly disease. The Schematic representation of the brain tumor microenvironment, displaying key cell types and signaling pathways is shown in Figure 1.

I. Brain Tumor Biology and the Role of the Microenvironment

Brain tumours represent a diverse entity of tumourscharacterised by dissimilar histopathological and molecular aspects as well as clinical factors [15]. In adult patients, gliomas are the most common and dynamic type, and they comprise a great majority of the malignant primary brain tumours, mainly the glioblastoma multiforme (GBM)[16]. Astrocytomas (originating in the astrocytic glial cells), oligodendrogliomas, ependymomas, and medulloblastomas (which occurs most frequently in children and young adults) are also common entities[17]. The variation between such diagnoses can be traced to the cell of origin, genetic causative agents, growth model, reaction to treatment and patient outcome[10]. In another example, GBM is associated with rapid growth, high invasion, apoptotic resistance, and intense genetic instability which frequently translate into very poor prognoses with little hope of median survival of over a year despite multi modal aggressions [18]. Astrocytomas are differentiated by grades I-IV; they manifest relatively nonmalignant courses in the low grades and can harbour the possibility of malignant transformation [19]. The malignant brain tumour that prevails in youngsters is medulloblastoma, a primitive neuroectodermal tumour that is characterised by the disruption of neurodevelopmental and oncogenic signals simultaneously[20].

Tumor Microenvironment Components

- Modern neuro-onco has given specific consideration to the tumor microenvironment (TME), an advanced and heterogeneous conglomeration of non-cancerous cells and extracellular matrices that have significant influences on tumor metastases and poor response to treatment[21]. In the central

nervous system, key components of the TME include the following:

- **Stromal cells :** Components of the tumor microenvironment that include the astrocytes, oligodendrocytes, pericytes, and cancer-associated fibroblasts are stromal elements. The said cells produce growth factors, cytokines, and matrix components that alter the behavior of the tumors and alter the response of drugs[22].
- **Immune cells:** In adult gliomas and other tumors of the brain, microglia (the indigenous macrophages of the brain), blood macrophages, T cells, and, in some cases, dendritic cells are found in the tumor tissue. They also often get programmed by tumoral signals to be immunosuppressed or even tumor-promoting cells[23].
- **Vasculature:** Malignant brain tumors are characterized by having abnormal blood vascular systems. The angiogenesis of tumors is promoted by other factors like VEGF (vascular endothelial growth factor) and enhances the rapid growth of the tumor, but also changes both the physiological and anatomical integrity of the blood brain barrier (BBB), leading to tumor growth as well as immune system evasion[24].
- **Extracellular Matrix (ECM):** ECM is the scaffold on which both tumor and stroma components reside and its content- such as tenascin-C, laminins, and hyaluronic acid- is rearranged by tumor produced enzymes (such as MMPs) facilitating invasion and resistance to treatment[25].

Tumor-Microenvironment Interactions

Brain tumor cells and their TME have a significantly reciprocal and dynamic relationship. The malignant cells secrete cytokines, chemokines and others that re-educate adjacent stromal and immune cells to acquire new phenotypes that contribute to tumor growth, survival and metastasis. For instance:[26]

- There is a possibility of astrocytes around glioma cells changing to the reactive status where they secrete factors to facilitate increased proliferation and invasion of tumor cells[27].
- Tumor-infiltrating macrophages (or microglia, TAMs) are shifted away toward the classical (M1) anti-tumor status into the different (M2) profiles that secrete growth factors, enzymes modifying the surrounding matrix, immunosuppressive cytokines and lead to the creation of a favorable climate to tumor development and the reduction of productive anti-tumor immunity[28].
- Remodeling of ECM leads to the release of latent growth factors, whereas the signaling by integrins between the tumor cells and ECM proteins stimulates the pro-survival and migration pathways[29].
- Angiogenesis not only makes abnormal channels of vascular supply but also generates particular impediments against immune cell mobilization and drug/therapeutic access[30].

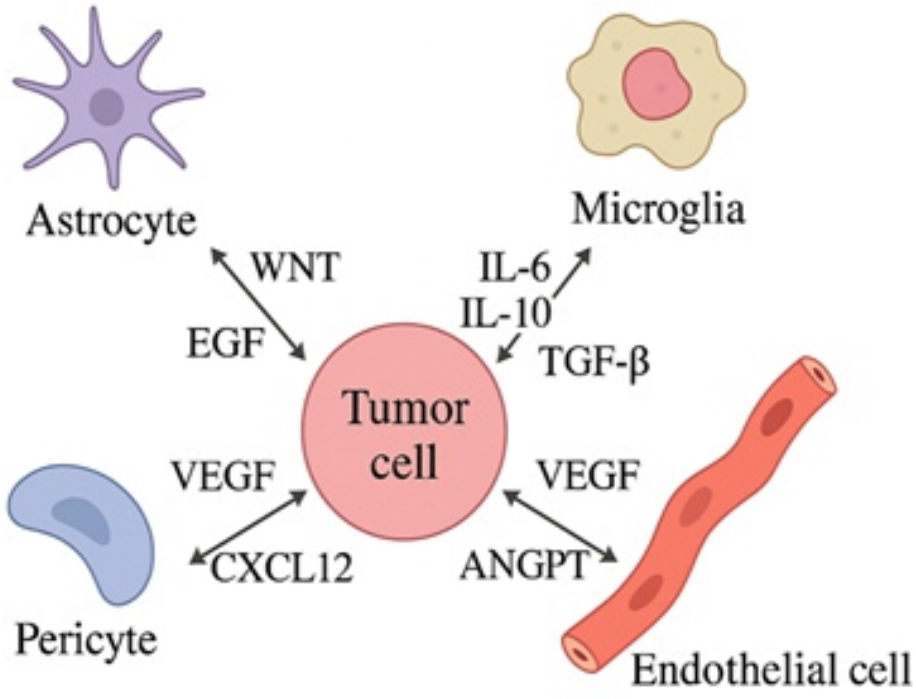

Figure 1: Schematic representation of the brain tumor microenvironment, displaying key cell types and signaling pathways.

This is a schematic diagram of the complex microenvironment of brain tumors, in which the interaction of tumor cells with major types of surrounding cells is emphasized, namely, astrocytes, microglia, pericytes, and endothelial cells. There is Bidirectional signaling pathway in which molecules of VEGF, EGF, IL-6, IL-10, TGF-b, WNT, CXCL12, and ANGPT are very important in tumor progression, immune response regulation, angiogenesis and intercellular communication. Investigating those complex signaling systems is the key to treatment with the target interruption of tumor-fostering relationships in the brain.

II. THE MICROENVIRONMENT'S INFLUENCE ON TUMOR PROGRESSION AND THERAPY RESISTANCE

Recent developments show that tumor microenvironment (TME) is a crucial factor in propelling the growth of brain tumors, heterogeneity and resistance to therapies [31]. The TME is made of stromal, immune, and vascular elements and is in a dynamic reciprocating interaction with tumor cells and functions to regulate essentially every cancer hallmark [32]. This section includes comments on some key molecular paths molded by TME hypoxia, angiogenesis, immune evasion and evaluates how components of TME support treatment resistance and clarifies the intricate cross-communications which synthesizes these consequences. The Major signaling pathways and factors in the TME that contribute to brain tumor growth and drug resistance is shown in Table 1.

1. Molecular Pathways Influenced by the Tumor Microenvironment

a. Hypoxia and Cellular Adaptation

As a result of proliferation of solid brain tumor, particularly glioblastoma tumors, the cell proliferation rate outstrips the vascular rate, thus creating a focal area of chronic hypoxia[33]. In this context, hypoxia-inducible factor 1-alpha (HIF-1alpha) will have its stability increased, and transcriptional program through which HIF-1alpha acts includes angiogenetic molecules, glycolytic genes and elements involved in cell survival and invasion[34]. These reactive compensations of the tumor microenvironment are hypoxia mediated, i.e.; exercise the following:

- The upregulation of vascular endothelial growth factor (VEGF) in the local microenvironment, as well as other pro?angiogenic factors, that are upregulated in parallel, triggers the development of abnormal, pathological vasculature[35].
- Re-programming of the metabolism in the glycolytic way, similar to the Warburg effect, which allows them to provide energy even in the condition of oxygen debt[36].
- Epithelial-mesenchymal transition (EMT) is typified with raised expression of genes mandating last cells-epithelial cell vicinity-approach to a mesenchymal one. This is a biological process which enables epithelial cells to gain the ability to migrate and attack other cells like mesenchymal cells and is the process which induces both intravasation and metastasis[36].

b. Angiogenesis and Vascular Dynamics

Angiogenesis, which is the novel formation of vessels on basement of quite old vascular systems, is one of the key processes involved in the process of tumor survival and development [24]. The tumor microenvironment contributes to this activity by producing pro-angiogenic factors like vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietins[24]. Signaling molecules stimulate and direct these endothelial cells to remodel and multiply, hence creating a disorderly, leaky, and an inefficient blood vascular network inside the brain tumor[37]. This network has a constant delivery of nutrients and oxygen to facilitate the growth process of tumor but at the same time increases the interstitial pressure and reduces perfusion, thereby worsening the hypoxic condition. In addition to that, the type of vascular architecture makes a physical and functional blockade on the movement of immune cell inside and around it, thus affecting the delivery of drugs to the abnormal site[38]. Although such therapeutic angiogenesis targeting by agents like bevacizumab have clinically shown benefit, especially in cases of recurrent glioblastoma, the effects are usually temporary due to the adaptive measures involved with microenvironment thus bypassing the anti-angiogenic mithigation and promoting therapeutic resistance[39].

Immune Evasion and Immunosuppression

Malignant neoplasms are sculpts actively developing their microenvironment, thus producing an immense impact on the immune environment of the tumor[32]. The key element of this modulation is the appearance of tumor-related macrophages and microglia (TAMs), the predominant polarization of which to the M2 phenotype occurs[40]. One

phenotypic switch that has been found in many cell lines is the exaggerated change to an increase in the production of anti-inflammatory and immunosuppressive molecules in particular interleukin-10 (IL-10) and transforming growth factor-beta (TGF-beta)[41].These mediators seem to promote tissue remodeling, but on the other hand prevent the formation of effective anti-tumor immune responses. At the same time, the TME programs the growth of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) cells, with profiles that suppress the activity of cytotoxic T lymphocytes (CTL)[42]. It is also found that stromal and cancer cells also up-regulate the immune checkpoint molecules like PD-L1, therefore stimulating the depressive receptors on the T cells and effectively reducing cytotoxicity[43]. Also, the excessive concentrations of extracellular adenosine and other immunosuppressant metabolites found inside the TME affect the functionality of immune cells[44]. The combined effects of these processes result in a setting that promotes tumor escape immune-surveillance, as well as development of therapeutic refractoriness[45].

2. Mechanisms of Therapy Resistance Mediated by TME Cells

a. Physical and Biochemical Barriers

At the molecular level, the cerebral endothelium is an insurmountable barrier since the blood brain barrier (BBB) places extremely narrow requirements on the vascular permeability and efficiently locks out the majority of materials present in the periphery[46].There is also an upregulation of efflux transporters particularly P-glycoprotein in the tumor microenvironment (TME) by the tissue-resident cells within the tumor environment; this decreases absorption of chemotherapeutic agents by passive diffusion[47]. At the same time, the extracellular space surrounding solid neoplasms develops a dense and gel-like nature with an increase of hyaluronic acid and tenascin-C, making it difficult to penetrate the drugs and promote the spread of tumor cells[48].

b. TAMs and Chemoresistance

The tumor-derived cytokines selectively polarize the tumor-associated macrophages (TAMs) toward M2 phenotype, discharge growth- and survival-enhancing mediators (e.g., EGF, VEGF), matrix-metalloproteinases and antioxidants which reduces the oxidative stress caused by the chemotherapeutic factors. Via experimental data, it has been determined that depletion or the reprogramming of TAMs can turnback the resistance phenotypes and result in improved therapeutics[49].

c. Stromal and Endothelial Cell Interactions

Stromal components, i.e., pericytes and, by extension, cancer-associated fibroblasts secrete paracrine cytokines, in particular, IL-6 and CXCL12, which guide transcriptional induction through the activation of STAT3 and the PI3K/Akt pathway, preventing apoptosis in tumor cells[50]. The NOTCH and other signaling pathways generated by the activation of the endothelium of tumor-specific vessels are capable of maintaining the populations of glioma tumor-initiating cells, a functional tumor cell subpopulationaters that is already characterized by its resistance to conventional therapies[51].

d. Hypoxia-Induced Resistance

Hypoxia in the TME has been linked to changes of metabolism and production of anti-apoptotic proteins (e.g., Bcl-2, survivin) that suppress radiotherapy and most cytotoxic agents[52]. Hypoxia also enhances a stem like phenotype, as more slowly dividing, and refractory to therapy, cells survive when the first debulking of a tumor is successfully done[53].

3. Crosstalk Between Tumor Cells and the Microenvironment

a. Paracrine Signaling Loops

An example of paracrine correlations among cells of the TME is possibly the sheer number of connections betwixt the non-malignant and malignant inhabitants of the brain:

Tumor cells produce colony-stimulating factor 1 (CSF-1) and CCL2 that recruits and polarizes myeloid cells which subsequently produce cytokines, and growth factors to promote tumor growth and invasion[54]. In co-culture conditions of cancerous cells with astrocytes, the cellular processes contribute to resistance to cytotoxic pharmaceuticals through gap junction-mediated relay of cyclic GMP-AMP and secondary signalling messengers[55].

b. Matrix Remodeling and Invasion

Tumor and stromal cells collaboratively secrete matrix metalloproteinases (MMPs) that degrade the ECM, facilitate tumor cell migration, and liberate growth factors. ECM-integrin signaling further activates tumor cell survival and pro-invasive pathways[56].

c. Stem Cell Niches

The perivascular niche is an independent microenvironment that supports the existence of populations of the glioma stem-like cells (GSCs). This system would be defined as endothelial, pericyte and soluble signal network, which guide the coordination of stem-like phenotypes in gliomas.[57]The constant bidirectional signalling between these cellular constituents and the extracellular environment maintains the stem phenotype, endows the cells with therapeutic resistance and represent a source of recurrent disease even after therapy[58].

4. Implications and Opportunities for Therapy

The idea of the TME being central to the process of brain tumor development and resistance to therapy treatment has been the key to the development of new approaches targeting not only the tumor cells but also their supporting and protecting habitat. Therapeutics are in development and evaluation to target angiogenesis-reducing, immune-reprogramming, stroma-derived paracrine signal-inhibiting and ECM-modulating therapeutics. The predictive biomarkers of microenvironment features could avert the gambit, choosing the patients who could profit the most out of such treatment.

Drug Name	Mechanism of Action	Trial Phase	Outcomes	References
Bevacizumab	Anti-VEGF monoclonal antibody, inhibits angiogenesis	Phase III/IV	Improved progression-free survival, limited overall survival	[59]
Nivolumab	PD-1 checkpoint inhibitor	Phase III	Modest efficacy in glioblastoma, ongoing research	[60]
CAR-T cells (GD2-targeted)	Engineered T cells targeting GD2 antigen	Early Phase I/II	Some tumor regression, early safety data	[61]
Metformin	Metabolic pathway modulator, inhibits glycolysis	Phase II/III	Investigational, potential radiosensitizer	[62]
Cilengitide	Integrin inhibitor targeting ECM interactions	Phase III	Failed to improve survival in phase III	[63]

Table 1: Major signaling pathways and factors in the TME that contribute to brain tumor growth and drug resistance.

III. PHARMACOLOGICAL APPROACHES TARGETING THE TUMOR MICROENVIRONMENT

The Overview of main pharmacological strategies targeting the TME in brain tumors are shown in Figure 2 and recent clinical trials of pharmacological interventions targeting the TME in brain tumors are shown in Table 2.

1. Anti-Angiogenic Agents and Vessel Normalization Strategies

The creation of new blood vessels, angiogenesis, is the centerpiece of the growth and survival of brain tumors, particularly the malignant types such as glioblastoma. VD is well-understood to be an active promotion of the tumor microenvironment (TME) and primarily through vascular endothelial growth factor (VEGF) and correlated signaling pathways[64]. The potential therapeutic effects of anti-angiogenic agents on aberrant vasculature are inhibited through interaction with VEGF-A, especially with the monoclonal antibody known as bevacizumab[65]. There are also other types of agents like tyrosine kinase inhibitors, which disrupt a variety of pro-angiogenic signals. These agents have a potential to normalize the existing tumor vasculature so as to temporarily increase the functional capacity of both existing and potential improvements in the delivery of synchronous agents[66].

2. Immunotherapy Approaches

Immunotherapy has become one of the promising modalities in treatment of brain-tumors that has tried to unleash a useful host defense against tumors, which are unnaturally not

robustly immunogenic[67]. Checkpoints inhibitors adapt the peripheral and intratumoral immune repercussions of the tumor microenvironment (TME) via restraint of programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), as well as cytotoxic T- lymphocytic antigen-4 (CTLA-4)[68].Nonetheless, the impact of tumors in the central nervous system (CNS) on these agents has been limited in efficiency, and this fact can probably be attributed to the hyper-immunosuppressive TME, low tumor mutational burden, and physical barrier to the blood-brain barrier. Clinical trials in progress thus continue evaluating combination regimens, and optimizing identification of patient subgroups that would be likely to obtain great benefit[69]. Chimeric Antigen Receptor (CAR)-T cell therapy consisting of genetic modification and expansion of a human patient T cell with recognition of tumour-specific antigens has shown promising early signs, especially against new targets like GD2 in diffuse midline gliomas, where some patients have recorded significant tumour shrinkage[70]. In light of the fact that transport of immune-cells across blood brain barrier has been an issue, CAR-T cells would often be introduced directly in the tumor or into the cerebrospinal fluid compartment[71]. Further, in line with this, there are the cancer vaccines, such as the peptide- and dendritic-cell-based preparations that have been used to stimulate and boost tumor-specific T-cell responses but despite the reported immune activation in the preclinical/early phase study, clinical efficacy across the board and sustained response has not been achieved[72]. Comprehensively, these immunotherapeutic methods represent a fast-developing area with a significant potential, but addressing the characteristic suppression immanent to the intrinsic microenvironment of brain tumors remains the major challenge.

3. Agents Targeting Metabolic Adaptation, Stromal Modulation, and Extracellular Matrix

Metabolic Adaptation:

Tumor cells in the tumor microenvironment have strong metabolic reprogramming that mainly includes Warburg effect (aerobic glycolysis) and parallel alterations in nucleotide, lipid, and iron metabolism[73]. These changes maintain tumor growth and, in addition, cause resistance to conventional treatment. Such agents as metformin traditionally used for anti-diabetic use but now under evaluation as adjuvant therapies to radiations and chemotherapies are active in sensitizing tumors. Other agents affecting the metabolic pathways are also under evaluation. The substantial metabolic heterogeneity and cross-subtype variability of tumors are signs that there can be no single method that works on any cancer[74].

Stromal Modulation:

Growth of neoplastic tumors is based on the interactions between the malignant cells and the related stroma[75]. The tumor-related stromal cells (such as astrocytes, fibroblasts, and pericytes) sustain the viability of the tumor and tumor expansion by means of producing cytokines as well as paracrine signaling[76]. Based on this, researchers are coming up with the specific agents that can interfere with cytokine-based pro-tumor pathways. The most prominent of these are small-molecule inhibitors of the IL-6/STAT3 and CXCL12/CXCR4 signaling axis, thereby regulating different elements of the neoplastic stromal soil that promote neoplastic seeds[77].

Extracellular Matrix (ECM) Targeting:

Both brain tumor extracellular environment and extracellular matrix are scaffold and a powerful regulator of tumor growth. Based on that, the ECM is a crucial therapeutic target as it is involved in tumor invisibility, drug resistance, and immune trafficking of cells[32].The already available pharmacological solutions to ECM include matrix metalloproteinases (MMPs) inhibition, which enzymes play a critical role in ECM degradation and remodelling thus blocking tumor invasion and metastasis[78]. Moreover, also integrin antagonists have been used to interrupt cell attachment along with the resultant signaling channels, which are involved in the growth of tumor, as well as, migration and survival[79]. Monoclonal antibodies, RNA interference work, and experiments using small-molecule inhibitors have looked at direct targeting of ECM proteins upregulated in high-grade gliomas CSPG4/5, PTPRZ1, SDC1, TGFBR3, PLG, GPC2, with the purpose of interfering with their pro-tumorigenic aspects. The alteration of the composition or the architecture of the ECM is also a good strategy to enhance the permeation and efficacy of immunotherapeutic agents and conventional chemo-therapies by overcoming physical and biochemical barriers

inside the tumor niches and hence it creates an attractive option of optimizing the outcomes of the aggressive brain tumor treatment[80].

4. Overcoming Drug Delivery Challenges: The Blood-Brain Barrier (BBB)

This challenge of the blood-brain barrier (BBB) is a significant structural and functional barrier to systemic entry of drugs into the CNS such that scientists have been forced to develop innovative ways of overcoming the barrier to increase therapy[81]. One of them is the temporary opening of the BBB. Osmotic approaches of opening tight junctions and allowing passage of drugs such as mannitol infusion, focused ultrasound targeting and electroporation are all classical approaches[82]. Carriers that consist of nanotechnology, i.e., nanoparticles, liposomes, and exosomes mimetics, present a different promising route[83]. They utilize processes that transport across the BBB through a mechanism such as receptor-mediated transcytosis, membrane camouflage to transport their cargo across the BBB, and protect the therapeutic load, enhance targeting, and enhance pharmacokinetics[84]. The intranasal route has been considered a noninvasive alternative since drugs can travel directly to the brain by using the olfactory nerve[85]. Additional chemical modifications and attachment of ligands to aid with crossing the BBB are also used to increase the permeability and targeting receptor-mediated transport[86]. All these approaches take the field of CNS drug delivery a step forward, and they should be sensibly considered against their efficacy and the possible neurotoxic effect, the invasiveness of the process, and the technical complexity[87]. Therefore, the contemporary trend in drug development is the focus on the development of drugs that can breach BBB, thus maximizing the treatment of brain tumors.

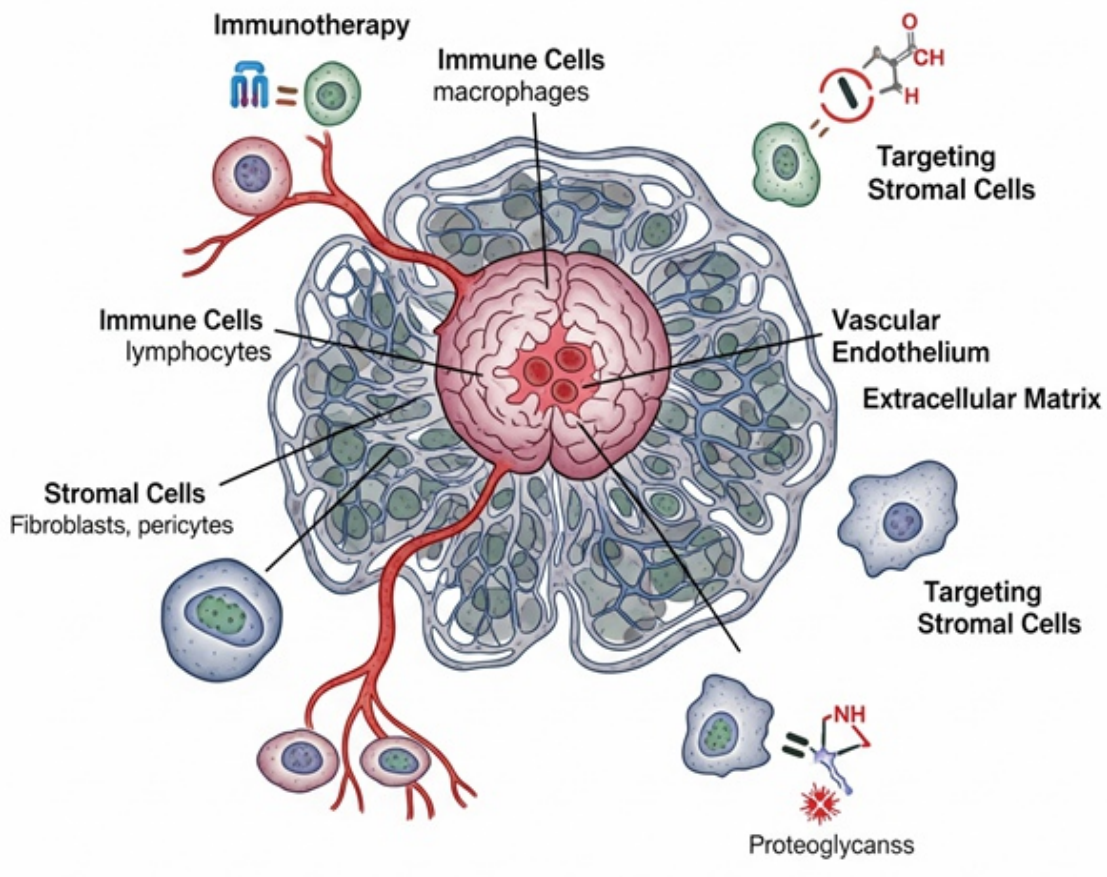

Figure 2: Overview of main pharmacological strategies targeting the TME in brain tumors.

This picture depicts pharmacological tactics against the Tumor Microenvironment (TME) in terms of brain tumorous other conditions. It brings to the fore how new agents that would target disrupting major components of the TME, such as immune cells, stromal cells, vascular endothelium, and extracellular matrix are targeted in order to improve therapeutic outcome

Brain Tumor Type	Cell Origin	Typical Age Group	Prognosis	Common Molecular	References
Glioblastoma Multiforme (GBM)	Astrocytic glial cells	Adults, 45–70 years	Poor, median survival 15–18 months	EGFR amplification, PTEN mutation, IDH wildtype	[88]
Astrocytoma	Astrocytic glial cells	Varies by grade, often adults	Variable by grade, from indolent to aggressive	IDH mutations in low-grade, TP53	[89]
Medulloblastoma	Primitive neuroectodermal cells	Children and young adults	Variable, often treatable with therapy	WNT and SHH pathway mutations	[90]

Table 2: Recent clinical trials of pharmacological interventions targeting the TME in brain tumors

I. EMERGING THERAPIES AND FUTURE DIRECTIONS

Over the last few years, there has been a large growth in new courses of action and emerging strategic models which are separately focused and aimed at curbing ongoing impediments in the management of brain tumors. The area of this growth has been in a greater targeted aim of the tumor microenvironment (TME). Separately designed small molecules such as the next-generation of kinase inhibitors, epigenetic modulators, and molecules that interfere with the metabolic pathways are under development that target the molecular vulnerabilities in high-grade gliomas and other brain neoplasms that have been identified previously in those diseases and are often characterized by better blood-brain barrier (BBB) penetration and enhanced safety profiles. The development of biologics, in particular monoclonal and bispecific antibodies, has brought an enormous light into the accuracy of the immune modulation; they are able to target tumor antigens and the microenvironmental containment at the same time. Simultaneously, delivery systems based on nanoparticles (including liposomal and exosome mimesis) are in an era of fast technological advancement, to the extent that, given their ability to deliver multiple payloads (chemotherapeutic agents, RNA species, and imaging probes) across the BBB with little systemic toxicity, and with optimization of pharmacokinetics, they are emerging as the most important technology in the field. Improved vectors used to deliver gene therapies by viral and non-viral vectors open up the possibility to deliver suicide genes, immune stimulants, or genome-editing constructs intratumoral or within the CNS; these same modalities have been shown to be feasible and biochemically efficacious in gliomas in early-phase clinical trials. Altogether, all these developments can be seen as a shift to more complex and precision-based treatment strategies targeting TME of brain tissues. The Pipeline of emerging pharmacological agents targeting TME components are shown in Figure 3.

New disease combinations with cancer are often combined with the conventional ways of cancer treatment, e.g., radiation and temozolomide, in rational combinations that aim at both decreasing tumor burden and controlling protumorigenicity factors of the microenvironment.

Personalized medicine has now taken its position in the centre of this paradigm whereby longitudinal monitoring in genomic and transcriptomic data can then be used to stratify patients into therapeutic portions, iteratively adjust treatment with respect to the evolution of the molecular pathology, and pre-clinical strategies through organoid or patient-derived xenograft casting. However, there remains a big gap in clinical translation of laboratory success, which is characterized by a lack of durability, tumor heterogeneity, adaptive resistance in the tumor microenvironment (TME), insufficient predictive analytics, regulatory obstacles, and the logistic challenges of scale production of cell-based or personalized products. Consequently, any combination of new drugs and biomarker-integrated strategy promises to green-light a new era of brain-tumor treatment, whereas the continuation and expansion of multidisciplinary research into the forgotten hell of translational research are the bare minimum necessary to overcome the trepidation and fulfill the potential of an immunochromed tumor microenvironment.

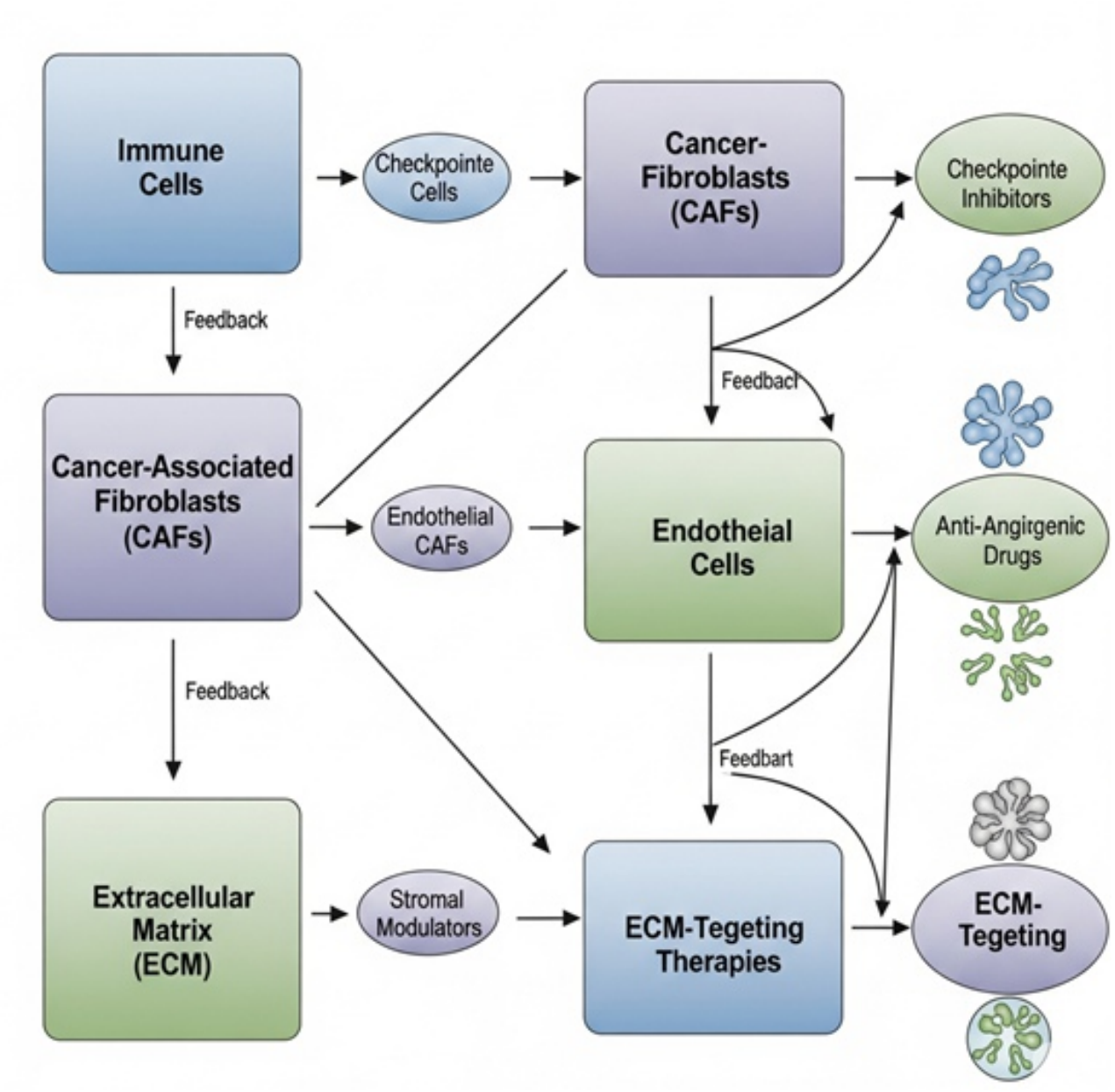

Figure 3: Pipeline of emerging pharmacological agents targeting TME components.

This image illustrates a pipeline of novel pharmacological agents with aim of targeting specifically the components of the Tumor Microenvironment (TME). It depicts the complicated interactions of the immune cells, cancer associated fibroblasts (CAFs), endothelial cells and extracellular matrix. The scheme indicates how a number of therapeutic approaches, such as checkpoint inhibitors, anti-angiogenic agents, and ECM-based therapies, are being designed to interfere with such facilitating tumor environment. The purpose will be to eliminate resistance and enhance results on cancer treatment.

V. LIMITATIONS AND CHALLENGES

Although there has been significant advance in the understanding of tumor microenvironment (TME) in brain tumor to be used as a therapeutic anchor, there are other barriers being actively put forward [91]. The essential aspects of this list is the rich inner-diversity of both brain tumors and the microenvironment that surrounds these tumors. Take glioblastoma, it is not a homogeneous mass, but rather, it is a heterogeneous cellular sub-population that have different genetic and epigenetic signatures, subsequent metabolic phenotypes and phenotypic behaviours[92]. This heterogeneity is also represented by the TME in which the distribution of stromal cell types and behavior, immune cell infiltration and circulation as well as vascular morphology show interpatient, intertumoral, and even intratumoral and interregional variability[91]. As such, one component of cell or molecular population-based interventions has a higher likelihood of evading other components, requiring multi-focal or adaptive treatment regimens to compensate the plasticity inherent in tumor and the TME[93].

The greatest challenge to progress in neuro-oncology is that the current pre-clinical research models do not encompass the multifaceted assembly of the human brain tumor microenvironment (TME)[94]. Most of the laboratory studies rely on in vitro cell culture model systems or murine xenografts; these models offer invaluable systems to the understanding of mechanism and offering the ability to perform an early stage screening of drugs, but these models are ill-positioned to capture all the aspects of the human TME, the brain parenchymal architecture, inter-species immune interaction, and intricate combination of a neoplastic cell and its microenvironmental environment[95]. Besides, very few animal models are able to replicate some of the known properties of the human bloodbrain barrier (BBB) or the immune-suppression of human neoplasia.

VI. CONCLUSIONS AND RECOMMENDATIONS

Recent advances in the treatment of brain tumors favor the significance of therapeutically directing tumor microenvironment (TME), and represent a critical shift of tactics that relies entirely on tumor cell-centric practices. The present approaches are directed to the regulation of angiogenesis, reconstruction of immune and stromal elements and overcoming the blood-brain barrier restrictions. Such efforts have come up with very diverse pharmacological actions that include anti-angiogenic agents, immunotherapies, metabolic and extra-cellular matrix modulators. New ways cover the field, including the field of gene therapy, nanotechnology-controlled delivery, and personalized medicine, which have increased the arsenal even more. Although there has recently been a flood of progress regarding cancer genomic research, the immense variability of patients serves as an impediment in the analysis of tumor and tumor microenvironment (TME) complexity.Going further, the future outlooks warrant effective patient stratification based on multi-omic profiling; optimization of preclinical models that are physiologically resembling human tumors; and development of a set of adaptive therapeutic regimens that can respond to the dynamic environments of tumors.The area of brain tumor management has been determined to have persistent gaps within both clinical practice and research. The areas of gaps include the potential tools in the form of robust biomarkers that can predict therapeutic response as well as monitor the progression of the tumor in a noninvasive manner, development of therapies that can help overcome the treatment resistance and toxicity, and methods that can help in longitudinally assessing the tumor microenvironment. It is only by a cyclical process between laboratory research and clinical practice that new interventions are carried through into sustainable clinical value in patients with brain tumor-enhancing life expectancy and the quality of life of patients.

Conflict of Interest

None

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None

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