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Glioblastoma and its Microenvironment

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Abstract

Background: Glioblastoma is the most common and aggressive primary brain tumor in adults. It is characterized by its highly invasive nature and resistance to current treatment strategies. The microenvironment of glioblastoma plays a crucial role in tumor progression and therapeutic resistance. It is essential to understand the complex interactions between tumor cells and their surrounding microenvironment to develop more effective treatment strategies.

Methods: For our literature search, we included all clinical trials, basic science publications, and experimental studies for review from inception until December 30th, 2021. We employed the following databases for this search: PubMed Central, MEDLINE, ClinicalTrials.gov, EMBASE, and Web of Science. Our search strategy involved using a variety of keywords, including 'glioblastoma', 'glioma', 'microenvironment', 'niche', 'immune', 'brain perivascular niche', 'glia stroma', 'exosomes', and 'microglia'. All full-text articles that met the search criteria were thoroughly reviewed for data collection, and structured and detailed notes were compiled.

Results: This literature review aims to provide an overview of current research on glioblastoma and its microenvironment. The Tumor Microenvironment (TME) has both gliogenesis and neovascularization properties. Astrocyte-like and oligodendrocyte-like cells are also important for the biology of the tumor cells. Immunotherapies are currently being researched and tested in glioblastoma patients as primary or salvage treatments.

Conclusion: The interactions established between glioblastoma and its microenvironment have emerged not only as hallmarks of tumor aggressiveness, but also as a non-negligible reason for treatment failure. Although extensive knowledge exists on the molecular alterations characterizing glioblastoma and its vascular/tumor interface, the contribution of conventional therapeutic approaches in shaping the complex tumor/microenvironment crosstalk has been only marginally elucidated, and this delay represents an additional piece in the disappointing outcome of currently adopted treatment. To reach a response rate adequate to support the application of conditional immunotherapeutic responses, additional data is expected on alternative toxic but selective therapies that boost or synergize with the novel approaches in trials.

Introduction

The microenvironment of glioblastoma is represented by the Blood-Brain Barrier (BBB), surrounded by a peculiar and silent region called the "peri-necrotic" area, and an extremely immunosuppressed Extracellular Matrix (ECM), reinforced by the so-called "hyperplastic" or "reactive" and "hypoxic" gliotic scar [1-3]. Collectively, this is a dual niche that shelters the rapid-plastic population of Glioma Stem Cells (GSCs) from micro-environmental pressures due to either hypoxia and/or inflammation and/or immune response [4,5]. These pathological features and niche specialization of the CNS make glioblastoma one of the main issues in once-neurology, which needs an urgent solution for therapeutic translation [6,7]. This review is mainly aimed to describe the interactive molecular networks played by GB and its microenvironment for the maintenance of Cancer Stem Cells (CSCs) stemness and chemoresistance [8,9]. Glioblastoma, classified as grade IV astrocytoma by the World Health Organization (WHO), represents the most common and aggressive primary brain tumor, accounting for 48% of all malignant primary brain tumors worldwide [10]. Surgical resection, an aggressive combination of chemotherapy with the alkylating agent, temozolomide, and radiotherapy, followed by adjuvant temozolomide, remains the current standard of care that has accompanied

substantial improvements in the overall survival of patients with glioblastoma [11,12]. Nevertheless, the majority of glioblastoma patients eventually develop progressive recurrent tumor growth, primarily due to the inevitable drug resistance and therapeutic evasion of tumor cells [13]. Nevertheless, glioblastoma is highly vascularized, characterized by a markedly aggressive and invasive phenotype, and closely resembles a living sponge with pseudopodia and tentacles embedded and advancing into the local or distant brain parenchyma [14]. This clinical erosive pattern contributes to the impossibility of achieving a satisfactory radical surgical resection or conventional radiochemotherapy, which in turn leads to a mean survival of 12-16 months from initial diagnosis [15].

Glioblastoma: A brief overview

At a histological level, glioblastoma was until recently divided into four subtypes according to the morphological arrangement of their cells (oligodendroglioma, astrocytoma, and mixed oligoastrocytoma). This, however, has changed for these tumors and also for their lower-grade glial neighbors (anaplastic astrocytoma and oligodendroglioma) in the 2016 World Health Organization classification of the Central Nervous System [16,17]. Now, besides the previously adopted grading based on various histopathological parameters (degree of similarity with tissue of origin, vascularity for instance), glioblastoma multiforme and the rest of gliomas are graded also on the marks left in their genome by the most frequent and significant mutations in genes like: isocitrate dehydrogenases 1 (IDH1) and 2 (IDH2), TP53 (tumor protein p53), ATRX (alpha thalassemia mental retardation X-linked), and the two "telomerase reverse transcriptase" promoter (pTERT) [18-20]. Glioblastoma, better known as Glio-Blastoma Multiforme (GBM), falls under the umbrella of glioma, constituting the most common and aggressive primary brain cancer. According to statistics, only two to three of 100,000 persons worldwide experience GBM every year [21]. Glioblastoma is usually diagnosed between the sixth and seventh decade of life. As early as 1926, GBM was described as having a life expectancy at the time of diagnosis of only 13 weeks, and even today the median survival of GBM patients remains around 12-14 months. Reasons for GBM lethality are multifactorial and include: i) the high brain invasiveness of these tumors; ii) radio- and chemo-resistance; iii) their fast growth (a doubling time ranging from a few days to a couple of months), and iv) because they afflict the most complex, vital, and functionally plastic organ in the human body [22-25].

Epidemiology and incidence

In this section, we provide a detailed analysis of the epidemiology and incidence of glioblastoma. Despite some limitations and different classifications in other neuro-oncology WHO groups, GBM accounts for the vast majority of malignant astrocytic tumors and has a significant worldwide incidence. Men are more likely to develop a GBM than women [26,10]. The disease is most common among older adults, peaking in incidence among those aged 75-84 years, with about 34 cases per 100,000. Most cases of glioblastoma develop from an unknown cause. However, a small proportion of people who develop a glioblastoma have been known to be at an increased risk for the development of the disease due to a history of ionizing radiation, other cancers, immunodeficiency syndromes, or neurofibromatosis type 1, a genetic disease [10,21,27]. At the same time, glioblastoma seems to be less associated with occupational conditions in epidemiological studies published after 2000. The incidence of GBM has increased slightly in the last 10 years. Finally, the survival rates of GBM are consistently low across regions and follow a decreasing trend according to age, with 5-year relative survival rare in patients aged 45 years [28,29]. In line with this, a decrease in the annual percentage of GBM at diagnosis was observed. The overlap between diagnosed and deceased cases was close to zero, as many GBM patients had a short predicted survival time. These changes in tumor diagnosis may be due to modifications in MRI diffusion standards and imaging protocols over the years [30,31]. While medical and clinical therapies have evolved significantly over the past 40 years, the overall survival of patients with glioblastoma (GBM or WHO grade IV astrocytoma), the most common primary brain tumor in adults, has improved only slightly. Additionally, in the last decade, we have gathered a very detailed view of the heterogeneity and complexity of the pathological and genetic features of human GBMs, and it has become clear that the tumor-associated microenvironment (TAM) plays an unresolved role in their initiation and progression [32,33].

Pathophysiology and molecular characteristics

Interestingly, in many cases, the genetic changes highlighted involve epigenetic (i.e., DNA methylation) modulation of a gene, leading to a decrease or lack of the function of the inappropriate pathway. In addition, these genetic/epigenetic changes in GB trigger signaling pathways such as receptor tyrosine kinases, Vascular Endothelial Growth Factors (VEGF), mammalian Target of Rapamycin (mTOR) or the phosphatase and tensin homolog (PTEN), retinoblastoma (Rb) gene or p53 that control angiogenesis as well as the immune response [34,35]. As a consequence, abnormal GLI2 function induces the expression of numerous target genes that in turn promote GB growth. All these mechanisms could be new potential targets for therapies in GB treatment. There are many genetic and epigenetic alterations which characterize GB, some of which have been reported as hallmarks of GB, while many others are the subjects of ongoing study on different pathogenetic mechanisms. From a detailed analysis of available data reporting genetic and epigenetic changes, some powerful ancient pathways have been reconstructed in GB by different approaches. These analyses have shown the occurrence of genetic alterations regarding the cell cycle driving to uncontrolled proliferation and activation of oncogenes pressuring survival, and into immune-surveillance, apoptosis and necrosis escape. These genetic events generally activate signals which are passed along to a number of molecules that are core for keeping biological homeostasis (RB-family through p16INK4 and CDK4/6 activation; p53; p14ARF-Mdm2-p53 genes, PTEN-AKT; p21, among others) [36-39].

Due to the genetic and transcriptomic complexity of GB, tumors can be classified, according to the molecular markers, into subcategories which include Proneural (PN), Classical (CL), and Mesenchymal (MES) GB, or a hybrid pattern. A detailed description of the study of different strategies which aim to classify GB based on the modifications of its molecular signature is beyond the remit of this paper and it is not the subject of this review. However, it is important to say that these updated subcategories of GB (IDH-wild type), through TCGA classification, are key prognostic indicators and provide some insights into the possible differences in molecular behavior among different IDH-wild type GB subcategories [40,41].

The tumor microenvironment in glioblastoma

The cellular component of the tumor microenvironment, together with an abundant network of vessels making GBM a

vascularized tumor, consists essentially of Tumor-Associated Macrophages (TAM). GBM-modified vessels evolve to include areas of increased perfusion and hypoxic regions, suggesting the absence of a productive response. The tumor mass is heavily infiltrated by microglia-derived TAM within the brain, while a minor component is represented by macrophages residing in the systemic circulation blood. GBM-associated microglia display an immunosuppressive and pro-tumor phenotype and are mainly located within and surrounding the GBM inflammatory infiltrate, particularly in tumor areas demarcated by enhanced area contrast. Such areas are mainly found at the tumor edge and consist of positive expression of CD68 and do not show up on histopathological evaluation [42-44]. Glioblastoma (GBM) is the most common and aggressive primary brain tumor of the central nervous system in adults. Transcriptome analyses have highlighted the important role played by genetic and functional heterogeneity in GBM evolution. Indeed, therapies have so far shown poor response, with Cancer Stem Cells (CSC) and the tight relationship with the surrounding microenvironment playing a crucial role in tumor resistance, reducing efficacy, and promoting recurrence. Such a complex relationship is the result of the tumor architecture, which is not just an isolated mass of neoplastic cells but consists of Cancer Stem Cells (CSC), differentiated tumor cells, and several non-neoplastic cell types thoroughly infiltrating neurons, astrocytes, and microglia/macrophages. Moreover, the Extracellular Matrix (ECM) assays are associated with tumor cells, contributing significantly to tumor behavior and progression. In this review, we focus on distinct tumor microenvironment elements in GBM, their reciprocal interactions, and their potential role as targetable entities [27,45,46].

Cellular components

The TME provides the underlying scenario for the reconstruction of the blood-brain barrier and is central in the prioritization of the GSC as the seed cells of GBM angiogenesis. The regulation of GBM invasion by microvascular cell-GSC interactions is detailed. Astrocytes enhance GBM invasion. Reactive astrocytes are an invariable feature of glioma and have been shown to modulate the growth invasion and growth of GBM cells. The alteration of microglia is hypothesized to result in a reduction in the effects of GBM in the brain. The blockage between factors in the glioma local microenvironment is shown in chronic inflammatory reactions [47-49]. Astrocytes, differentiated neurons, as well as endothelial and neuroglial cells are prone to immune responses during glioma carcinogenesis. The TME has both gliogenesis and neovascularization properties. Astrocyte-like and oligodendrocyte-like cells are also important for the biology of the tumor cells. Cancer stem cells have substantial associations with pericytes, as well as neural and endothelial cells. Cancer-associated fibroblasts are critical for the formation and maintenance of the perivascular GBM stem cell niche. Glioma stem cells provide a niche as a cellular framework for a vasculogenic program engaged by the cancer-associated fibroblasts. Immune cells in the GBM TME impact the efficacy of standard treatments. Microglia and macrophages modify the TME to support the growth and invasion of cancer cells. Neurogenesis may contribute to the extreme cellular heterogeneity identified in GBM. Astrocytes, neurons, and oligodendrocytes signal through various factors, modulating distinct GBM cell subpopulations. Astrocytes further assist the invasiveness and capacity of GBM cells for neovascularization. Likewise, the neurovascular unit is important for the formation of viable GBM treatment targets [50-54].

Glioblastoma is the most common and aggressive primary tumor in the central nervous system. It harbors a neurovascular unit, besides the tumor cells, known as the Tumor Microenvironment (TME). Within the TME, there are diverse cell types, including cancer stem cells, cancer-associated fibroblasts, glioma-associated microglia/macrophages, neuron precursor cells, immune cells, and endothelial cells, demonstrating the heterogeneity of the cellular composition [55,56].

Extracellular matrix

The Extracellular Matrix (ECM) of a healthy person is made up of several kinds of proteins and polysaccharides, and it accounts for around 20% of the total volume of an adult human brain. Almost every facet of development and function is eventually impacted by the interactions between these macromolecules and neurons, astrocytes, and other cells. While other cell types in the brain contribute to the creation, maturation, and structure of Extracellular Matrix (ECM), fibroblasts and other mesenchymal cells are the only ones that produce and deposit ECM proteins in many other tissues. The stiffness of ECM proteins can also alter the rates of drug diffusion in addition to cellular physiology, while the Dynamic Contrast-Enhanced MRI (DCE-MRI) contrast agent can be used to estimate perfusion and vessel permeability or macrostructure [57,58]. Previous literature has highlighted that increased secretion of ECM components such as Hyaluronic Acid (HA), fibronectin, thrombospondin, and tenascin-C by glioma cells contribute to this change in ECM composition. Glioma cells can become more mobile and invasive due to an increase in fibronectin and HA in the Extracellular Matrix (ECM) and an increase in the expression of certain receptors and integrins on the tumor cell. Glioma cells, for instance, have the ability to express more CD44, the primary HA surface receptor that binds to Matrix Metalloproteinase 9 (MMP9) in the Extracellular Matrix (ECM). Tumor migration is significantly influenced by mesenchymal stromal cells (MSCs), a particular kind of ECM [59,60]. MSCs in the TME have the capacity to produce Metalloproteinases (MMPs) and cytokines including IL-6, CXCL1, and CXCL2, which aid in the breakdown of the extracellular matrix in the area. The local conformational angiotensin of ECM proteins can also be altered by GBM cells, as Lu et al. demonstrated via CD146 creation in new fibronectin fibers. These changes also extend to the glycosylation of the EGF receptor, which prolongs Akt phosphorylation and increases resistance to radio/chemotherapies. Major matrix metalloproteases over-expressed in GBM are also responsible for the vascular break-down, as ArginaseI-expressing GBM cells degrade collagen 4 to downregulate VEGF receptor. Vascular maturity and vessel cell-sequestration can also be achieved, where Tie2-expressing GBM cells create AngiopoetinII to link Tie2 receptor and promote vessel network integration and pericyte recruitment. The chondroitinases of this tier also break down the action of NG2 (a growth factor receptor) to upregulate migration and chemoresistance in GBM [61,62]. Overall, the ECM within the miniGBM may introduce important mechanical cues alongside its metabolic roles, according to current literature. The metabolic phenotypes of the tumor cells may help determine the dynamic changes as well, which will prevent separation in future work. The Extracellular Matrix (ECM) surrounding the tumor tissue is composed of structural molecules such as fibrous proteins (e.g., collagen and fibronectin), proteoglycans, and glycoproteins, which contribute to the tumor stiffness or plasticity and complex biochemical cues (e.g., growth factors, cytokines, and enzymatic proteins) that can help determine tumor cell response to various treatments. Collagens account for up to 70%

of the dry weight in GBM ECM, where collagen IV-rich basement membranes have been associated with angiogenesis while type I collagen can bind growth factors. Fibronectin and vitronectin are glycoproteins that can link integrins to type I collagen in the ECM, where they and tenascins can mediate adhesion and chemotaxis. Hard and compliant stromal tissues can promote and hinder cancer progression respectively due to their ability to segregate cells of different ECM preferences [61-63].

Immune microenvironment

Glioblastoma has a profound ability to interact with the immune networks through various mechanisms leading to immunosuppression. Central to immune evasion is the IDH wild-type status of GBM cells, characterized by a genetic and molecular background that underlies their capacity for rapid, relentless autonomous cell division. In this review, we present the immune cellular components involved in gliomagenesis and glioma growth with a particular focus on the interface between GBM and immune checkpoint modulatory signaling. We present further evidence of GBM-induced adenosine signaling which directs to an adaptive immunosuppressive immune microenvironment. We further propose a putative GBM-specific model of hyperactive inflammasome activity in the GBM secretome which is shown to upregulate immunosuppressive cytokine release with subsequent downregulation of effector responses favoring GBM survival [53,64-66]. Highly specific cellular, molecular signaling involved in GBM-induced immunosurveillance is presented and the implications for GBM-specific immunotherapy targeting the interplay between GBM and the immune component are discussed in detail. In establishing an image-guided biopsy diagnosis, a differential diagnosis for a glioblastoma should include lower-/higher-grade, IDH-wildtype astrocytic gliomas, or glioblastoma, and molecular pathology classification can be used to confirm the diagnosis and predict future biology and treatment [67,68]. Immunotherapies are currently being researched and tested in glioblastoma patients as primary or salvage treatments. The immune checkpoint inhibitors act systemically in enhancing immune responses, whereas dendritic cell vaccines and adoptive T cell therapy have local responses, thereby modifying the microenvironment. Glioblastoma is characterized by intact, but suppressed immune responses systemically as well as locally. Histologically, glioblastoma tumors are primarily hypointense to isointense compared to normal parenchyma on T1-weighted images and hyperintense on T2-weighted images, and are often enhanced after administration of gadolinium [69-71]. They are frequently hypocellular with areas of necrosis, and have significant mass effect and upward transtentorial or uncal herniation, ultimately contributing to increased intracranial pressure and coning. Studies have shown CD133+ or CD34+ cells are capable of differentiation into astrocytes, oligodendrocytes, and neurons, which are cell types that develop gliomas. Approximately 80% of gliomas are astrocytomas, 15% are oligodendrogliomas, and about 5% are mixed oligoastrocytomas. Further characterization of gliomas enables categorization into lower-grade (I/II) and higher-grade (III/IV) gliomas [72-74]. Malignant gliomas are codified based on histologic and genetic characteristics established by the World Health Organization. The preventative effect of aspirin was not distinguished uniformly and was consisted initially for ischemic stroke (prophylaxis), atheromatic disease, congestive heart failure, and peripheral arterial disease. Also, the highest dose of aspirin was examined and when administered at a lower dose, selective anti-inflammatory actions of aspirin have also been demonstrated [75-77].

Interactions between glioblastoma cells and microenvironment

The abnormal vasculature and immune evasion mechanisms tightly dictate the evolution of the GBM microenvironment, preserving the tumor from a tumoricidal immune system response and facilitating the establishment of a malignant phenotype. Not least, GBM preferentially relies on glycolysis and does not completely use the TCA cycle in tricarboxylic acid, with these alterations linked to hypoxia and acidosis maintenance and a mesenchymal sub-population appearance, richer in tumor-repopulating cells and capable of influencing the more differentiated proneural or classical GBM cells [14,78,79]. Each of these interactions is functionally not a linear altered event, but a dynamic back-and-forth transduction of information and reaction in which the single partners are co-evolving, influencing each other in turn. Only a deep comprehension of their interactions could lead to the discovery of new druggable and non-druggable targets, as well as resistance-related mechanisms [80-82].

The interactions between glioblastoma cells and the microenvironment are recognized to be pivotal in the network of factors that contribute to drug resistance and tumor progression. The invasive behavior of GBM cells is facilitated by their dialogue with the diverse components of the TME, and GBM is able to establish intricate, tumor-specific connections to the ECM, the vasculature/angiogenesis, and cells of the immune system. GBM compromises the brain vasculature and is known to contribute to the formation of hyperplastic, normal, and aberrant blood and lymphatic vessels invading and draining within the surrounding brain tissue. Furthermore, the cytotoxic immune system response is not fully operational in the brain partially due to the presence of an intact Blood-Brain Barrier (BBB) that can impair lymphocyte T-cell infiltration [83-85].

Angiogenesis and vasculature

Xenograft studies revealed that most of the growth and the angiogenic factor-induced protease activity is lost as tumors grow beyond a few millimeters in size and hypoxia develops. Beyond this size, tumors begin to give rise to necrosis that is evident as tissue cores when visualized histologically. However, within these necrotic cores, as well as in the surrounding viable tumor cells, there exists well-developed vascular structures. This is due to a complex interplay of cellular and molecular interactions with the surrounding tumor microenvironment, which itself is heavily modified by perivascular matrix proteins. This significantly complicates the mechanistics that underpin therapeutic anti-angiogenesis protocols, including the resistance that is developed in tumors towards endostatin treatment, despite promising xenograft studies. A focus of anti-angiogenic therapy has been in putting an end to all of the new blood vessel development and flow to the tumor. Inhibitors of the VEGF pathway, such as Avastin, have shown little reproductive clinical success acting in these aims to date. The rest of this review will focus on the large array of potential anti-tumor targets available by reassessing how the tumor and its vascular niche are mutually sustaining [86-90].

Folkman proposed in the 1970s that angiogenesis was important for the progression of solid tumors because the formation of new blood vessels provided a mechanism to supply the increasing nutritional demands for the rapidly dividing cells [91]. These newly forming blood vessels lacked the hierarchical organization of normal vascular structures and as a result were structurally and functionally abnormal. More recent evidence

has begun to reveal the extent to which the development of an intratumoral vasculature is increasingly complex. Hyperplastic proliferative budding is a direct result of endothelial cell stimulation and increases the size of a patchy and patchily structured tumor vasculature. When the tumor grows, areas of hypoxia will be supplemented with more hypoxic, necrotic clusters of cells as they are unable to establish any new blood vessels within this microenvironment. These hypoxic areas stimulate pro-angiogenic factors and induce endothelial cell migration and vessel growth into normoxic regions of the tumor [92-95].

Immune evasion mechanisms

In addition to this, the GB cells also play a role in the release of exosomes carrying programmed death-ligand 1 (PD-L1), which appears to be a key inhibitor of the PD-1 signaling prevention on T-cell function. To confirm this hypothesis, preclinical studies have shown benefits in combining an anti-PD1 antibody with an anti-CTLA4 antibody (ipilimumab) that binds to a dendritic cell-presenting antigen, which stimulates the proliferation of T-helper CD4+ and cytotoxic CD8+ T cells by preventing the negative signaling and apoptosis of these cells. It was only recently that the use of this combination in the management of GB was proposed [96-99]. The PD-L1 receptor is expressed on microglia, macrophages, and monocytes, which in principle may also be considered as a supporting factor for GB. The treatment of GB with PD-1 antibodies in preclinical studies resulted in the decrease of intratumoral Treg and M2 macrophages and the induction of a potent tumor-specific cytotoxic T-cell response, thus proving its efficacy in the GB model. Although the blood-brain barrier prevents the migration of antibodies, the PD-1 antibody was tested in humans by intra-arterial infusion and its efficacy is now under investigation [100-103]. Glioblastoma has unique mechanisms to evade the immune system, thus increasing its ability to progress and resist therapy. First, the main mechanism developed to evade the immune system's effect is related to the finding of both immune suppression and tolerance within the tumor, mainly in the tumor microenvironment. In respect to local immunosuppression, glioblastoma employs the recruitment of regulatory T cells that suppress excessive inflammation and adaptive immune responses, and reduce the population of cytolytic natural killer and natural killer T cells, which are directly involved in eradicating tumor cells or supporting T-cell function by releasing IFN-γ and facilitating dendritic cell activation. Moreover, the secretion of indoleamine 2,3-dioxygenase by both the GB cells and myeloid populations suppresses the T-cell response and post co-stimulatory signal between the tumor cells and immune cells [104-108].

Therapeutic implications and future directions

Future directions: Moving forward, more research in artificial intelligence will be exploited to explore the most promising fields of research, which are mainly encompassing several "-omics" areas. Finally, several efforts will be directed towards the development of therapies that would finally be transferred from a research laboratory where they are patented, to a clinical trial where their efficacy and impact on overall survival of GBM patients must be tested. Moreover, an effort will be put into testing these drugs in newly established in-vitro, in-vivo, and ex-vivo preclinical models after testing them for safety and efficacy in the lab. Efforts will be put into identifying novel drugs or novel combinations of already established drugs. Determining synthetic lethality, a model with amino acids degrader, will exploit any untapped potential in the GBM translational research field. Current investigation focused on targeting the microenvironment, finding new ways to create novel treatment approaches, with a reduction in side effect profile. A range of treatment strategies have been developed, including direct targeting of cellular components of the microenvironment, inhibition of signaling between glioma cells and the microenvironment, as well as anti-stromal anti-angiogenic agents. Literature shows that potential targets commonly include VEGF and other aspects of angiogenesis such as endothelial receptor kinases. Unfortunately, while many GBM patients respond to anti-angiogenic treatments, the response is generally short-term, with few patients achieving significant survival increases. As with any other target, intrinsic GBM molecular features and microenvironment capabilities may affect sensitivity to drugs. Thus, conducting clinical trials in well-defined, tighter patient strata until considerable results are achieved may help to validate this hypothesis. Upcoming research will be performed on artificial intelligence and will focus on identifying novel anti-microenvironment molecular targets.

Glioma cells, together with their surrounding microenvironment, could be seen as two branches of the same root, strictly related to each other. Their interactions rely on a constant dialogue of biological information that leads these elements to induce a strong cooperation. Several shared signaling pathways have been described as promoting tumor growth, especially during the development of resistance to a given therapy. These findings have led many researchers to explore not only the cancer stem cell hypothesis but also the idea that the stroma could have an impact on GBM morphology, biology, and response to anticancer therapies.

Current treatment strategies

The current approaches to brain tumor therapy include surgery, chemo-, and radiotherapy as well as targeted therapies. Surgery is almost always followed by chemo- and radiotherapy, unless contraindicated and is usually combined with chemoradiation regimens. Temozolomide is the most frequently used chemotherapeutic agent with a small but significant therapeutic benefit. The currently evaluated targeted therapies use either blocking antibodies or small molecules that either target growth factor receptors, intracellular mediators, angiogenic molecules, various cell surface molecules, stem-like pathways or immune checkpoints. However, due to many obstacles such as tumor heterogeneity or adaptive resistance, most drugs failed to prolong survival and still many of these pathways are discussed to significantly contribute to therapeutic resistance mechanisms. The antiglioma vaccination or oncolytic virus therapy concepts have the main idea to evoke antitumor immune responses. Despite the fact that GBM, especially at a late stage of progression exhibit immune suppressive characteristics, immunotherapy approaches are very attractive and promising for further development or successful combinations also in GBM treatment. Unfortunately, the results of anti-immunotherapy antibodies such as anti-PD1/PDL1 reported so far in clinical trials were quite moderate in the respective cohorts. The direct targeting of immune checkpoints, such as anti-CTLA-4, PD-1, or PDL-1 checkpoint antibodies in clinical trials still revealed only marginal benefit and adverse side effects. Therefore, recent therapeutic concepts include the combination of such therapies. Other clinical studies with toll-like receptor agonists such as poly I:C or the application of cancer therapies including oncolytic virus approaches including polio or oncolytic herpes simplex (HSV-1716) virus vaccination demonstrated remark-

able response improvements in such approaches. Glioblastoma (GBM) is the most frequent and malignant primary brain tumor. Initial treatment consists of surgery followed by chemo- and radiotherapy; however, GBM is even associated with poorer prognosis, a median survival time of 15 months from diagnosis, following state of the art standard of care. Operative management impacts only marginally survival time, but adequate surgical treatment of GBM increases the overall survival of patients compared to nonsurgically managed patients. Adjuvant chemoradiation extends the median overall survival by approximately two and a half months compared to surgery alone, with a median overall survival from diagnosis of eight and a half months. There are therefore still unmet medical needs and new treatment concepts are pursued.

Challenges and opportunities in targeting the microenvironment

Several opportunities may be exploited in targeting the microenvironment. One of the hallmarks of GBM is invasiveness, and cells such as microglia, macrophages, and mesenchymal stem cells are derived in part from different sources of GBM cells and cause GBM progression, including invasion. This suggests that the microenvironment may be exploited as a novel target for GBM therapy. GBM is among the most irradiated of tumors, and the tumor microenvironment has been shown to consider GBM cells resistant to radiotherapy. In particular, GSCs are considered more radioresistant than transit-amplifying cells (TACs) in the bulk tumor since they are enriched in radioresistant pathways and can repair DNA more efficiently than TACs. Populating the tumor microenvironment with radiosensitive cells might target radioresistant GBM cells at high and low radiotherapy doses. Thus, future efforts in pre-existing tumor microenvironment-directed drugs may need to consider the tumor killing potential of their targeted microenvironment stromal cells if co-administered with chemotherapy or radiotherapy.

Challenges in targeting the microenvironment: How to target the microenvironment? Modulating the tumor microenvironment of GBM is challenging given its great complexity involving multiple genetic, metabolic, and cellular components and their communication pathways. The question is how and if it is possible to change the microenvironment to increase the efficacy of GBM therapy. A potential way is to target signaling and communication pathways in the microenvironment. Several drugs targeting angiogenesis and the immune checkpoint have failed to show meaningful improvement in GBM, which leaves the question of whether the microenvironment is causally implicated in resistance to therapy in GBM.

Conclusion

While the complexity of glioblastoma prompts an evolution of personalized diagnosis and treatment, the new challenge of tumor microenvironment interconnection pushes scientific investigation toward laboratory-based models of glioblastoma niche. In this scenario, mini-brains and preclinical models retain their capability of closely resembling the histology of the surrounding normal brain and tumor mass. These models could give an added value for tailoring in vitro tests, also embracing the study of possible chemoresistance mechanisms. All together, these approaches offer a global vision of a possible boost in glioblastoma malignancy and an investigative suggestion on the appropriate potential target in the evolution of different molecular subtypes. The time is ripe to see the ventures begun and the benefits they bring forth. The interactions established between glioblastoma and its microenvironment have emerged not only as hallmarks of tumor aggressiveness, but also as a non-negligible reason for treatment failure.

The TME is largely to blame for the poor long-term prognosis of GBM and the limited effectiveness of the available therapies. The complex interactions between the TME's immunological and non-immune components are highlighted in this study. This interaction helps to create a diverse and adaptable Tumor Microenvironment (TME), which in turn raises the tumors' level of immunosuppression, invasiveness, and proliferation. The BBB, neurons, microglia, and Extracellular Matrix (ECM) are non-immune components that play a significant role in the changes that occur inside the TME. However, the bulk of the widespread tumor-promoting effects observed both inside and outside of the TME may be attributed to the immunological component, which is composed of macrophages, DCs, B cells, and T cells. Results have improved as a result of a number of therapy strategies that specifically target the TME, although these have been applied to a very small subset of individuals. The goal of immunotherapies such immune checkpoint inhibitors and peptide- and cell-based vaccines is to strengthen the adaptive immune system in order to encourage stronger anti-tumor responses. However, poor tumor immunogenicity and immunosuppressive stresses ultimately result in resistance to immunotherapies due to the interaction of several TME components.

Although extensive knowledge exists on the molecular alterations characterizing glioblastoma and its vascular/tumor interface, the contribution of conventional therapeutic approaches in shaping the complex tumor/microenvironment crosstalk has been only marginally elucidated, and this delay represents an additional piece in the disappointing outcome of currently adopted treatment. Nowadays, integrated therapy that combines conventional and innovative strategies that are able to shape the tumor microenvironment, together with active immunotherapy, is taking into account the necessity to address the complex biology of glioblastoma. However, to reach a response rate adequate to support the application of conditional immunotherapeutic responses, additional data is expected on alternative toxic but selective therapies that boost or synergize with the novel approaches in trials.

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