Journal of Neuroimmunology 357 (2021) 577633

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review Article

The multifactorial roles of microglia and macrophages in the maintenance and progression of glioblastoma

Rishabh Chaudhary [a,*], Rhianna J. Morris [b], Emma Steinson [c]

[a] Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Vidya Vihar, Raebareli Road, Lucknow, India
[b] Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3QT, United Kingdom
[c] School of Chemistry and Molecular Biosciences, The University of Queensland, St Lucia, QLD, Australia

ARTICLE INFO

Keywords:
Brain tumor
Glioblastoma
Microglia
Macrophage
Neuroimmune system
CAR-T therapy
Immune cells

ABSTRACT

The functional characteristics of glial cells, in particular microglia, have attained considerable importance in several diseases, including glioblastoma, the most hostile and malignant type of intracranial tumor. Microglia performs a highly significant role in the brain's inflammatory response mechanism. They exhibit anti-tumor properties via phagocytosis and the activation of a number of different cytotoxic substances. Some tumor-derived factors, however, transform these microglial cells into immunosuppressive and tumor-supportive, facilitating survival and progression of tumorigenic cells. Glioma-associated microglia and/or macrophages (GAMs) accounts for a large proportion of glioma infiltrating cells. Once within the tumor, GAMs exhibit a distinct phenotype of initiation that subsequently supports the growth and development of tumorigenic cells, angiogenesis and stimulates the infiltration of healthy brain regions. Interventions that suppress or prohibit the induction of GAMs at the tumor site or attenuate their immunological activities accommodating anti-tumor actions are likely to exert positive impact on glioblastoma treatment. In the present paper, we aim to summarize the most recent knowledge of microglia and its physiology, as well as include a very brief description of different molecular factors involved in microglia and glioblastoma interplay. We further address some of the major signaling pathways that regulate the baseline motility of glioblastoma progression. Finally, we discussed a number of therapeutic approaches regarding glioblastoma treatment.

1. Introduction

Glioblastoma (GB), a grade IV glioma, is by far the most virulent type of primary brain tumor in adults, primarily affecting the central nervous system (CNS) region (Chaudhary, 2021). The most remarkable characteristic of glioblastoma is its highly aggressive nature, which includes progressive tumor growth, diffuse invasiveness and high resistance to conventional therapies, leading to a brief survival time of about 15 months following the first diagnosis (Louis et al., 2016). GBs are primarily characterized by cellular pleomorphism, nuclear atypia, diffusive growth patterns, mitotic activities, micro-vascular growth, and necrotic cell death that serve as important diagnostic characteristics of GB (Urbanska et al., 2014). Such specialized properties are indeed the outcome of genetic alterations and the disruption of a number of essential molecular pathways, culminating in high resistance to chemotherapy (Wirsching and Weller, 2016). GBs are primarily comprised of a heterogeneous cluster of tumor cells and a variety of mesenchymal stem cells (MSCs), all of which eventually lead to the progression, metastasis, resistance and recurrence (Q. Wang et al., 2017). Mechanisms that facilitate GB cell resistance have recently been addressed, and it is also established that GB heterogeneity is a key factor in GB resistance resulting from associations amongst tumorigenic cells and tumor parenchyma bodies (Hambardzumyan et al., 2015a; Roesch et al., 2018). There are primarily two forms of tumor heterogeneity that coincide: (1) extrinsic and (2) intrinsic. Through a number of studies, it is now recognized that the intrinsic heterogeneity in tumors is characterized by the existence of cellular niches with different phenotypes. Thus, it is postulated that the occurrence of a sub-population of CSCs (cancer stem-like cells) is chiefly accountable for the intrinsic heterogeneity. Moreover, the expression of these distinct phenotypic traits is dependent on interactions with the tumorigenic environment. Such types of interactions result mostly from initiation of numerous cellular

* Corresponding author at: Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University (A Central University), Vidya Vihar, Raebareli Road, Lucknow 226025, U.P., India.
E-mail address: rishabh.smile19.rc@gmail.com (R. Chaudhary).

https://doi.org/10.1016/j.jneuroim.2021.577633
Received 26 March 2021; Received in revised form 26 May 2021; Accepted 11 June 2021
Available online 15 June 2021

mechanisms by receptors and their ligands, like cytokines and growth factors. These indigenous factors are very critical for the enrollment of parenchymal cells like astrocytes, microglia and endothelial cells that eventually invade the tumor, to aid in their growth, a process known as extrinsic heterogeneity (A. C.C. da Fonseca et al., 2012; Patel et al., 2014). Endogenous CNS cells such as microglia, oligodendrocytes, astrocytes, endothelial cells, neurons, and macrophages and/or monocytes are all adversely affected by GB cells (Broekman et al., 2018; Quail and Joyce, 2017). And, of all these cells, microglia and macrophages are by far the most prevalent cells in the brain tumor. GBs recruit neighboring resident microglial cells through the secretion of various chemokines and cytokines (W. Li and Graeber, 2012). According to flow cytometry and histopathological studies, the GB individual samples and animal biopsies have shown that these microglial cells along with infiltrating macrophages and/or monocytes can make up to 30-50% of the GB cell mass (Annovazzi et al., 2018; Anna Carolina Carvalho da Fonseca et al., 2014; Garcia et al., 2014; Olah et al., 2012; Roggendorf et al., 1996; Z. M. Zhang et al., 2015). The two distinct sources of microglia and macrophages inside the brain are: (1) parenchymal resident microglia and (2) monocytes/macrophages that access the brain from myeloid tissues. Based on the similarity of their surface marker expression and bioactivities, prior findings have asserted that both types of cells, microglia and macrophages, are derived from myeloid tissues. Recent studies, however, revealed that microglia and macrophages are two separate myeloid cells with distinct developmental backgrounds (Gomez Perdiguero et al., 2015; Schulz et al., 2012).

2. Microglia

2.1. Origin of microglia

Microglia are native myeloid cells of the CNS. They are referred to as glial cells. Their origin, however, is different from other glial cells. Microglia are phagocytic cells that reside in the brain and are derived from the yolk sac during early embryonic development (Fig. 1) (Ginhoux et al., 2013; J. G. G., 1933). Rio–Hortega and Asua, utilizing silver carbonate methodology, were the first to discover the presence of microglia in brain tumors in 1921. They found process-bearing cells in the CNS parenchyma and named these cells *"microglia"* (J. G. G., 1933). In 1925, Penfield published the first systematic framework of microglia and the phagocytosis mechanism of gliomas (Penfield, 1925). Ginhoux et al., used a pulse-labeling technique to differentiate yolk sac macrophages between embryonic day (E) 6.5 and 10 and discovered that microglial cells are derived from yolk sac macrophages present between E7.25 and 7.5 and infiltrate the embryo following vascularization on day 8, prior to primitive hematopoiesis in the embryo, based on the Runx-1 (runt related transcription factor-1) expression sequence (Ginhoux et al., 2010). However, there are other brain microglia ontologies that represent different phases of yolk sac hematopoiesis (De et al., 2018). Microglial cells can be found in extracerebral mesenchyme in humans as early as 4.5 weeks of gestation period and invade parenchymal tissue at about 5 weeks of gestation (Monier et al., 2006, 2007). Primitive haematopoiesis may also include precursors to the adult hematopoietic stem cell populations. The progeny of hematopoietic stem cells are accountable for the peripheral or circulating compartment of monocytes that

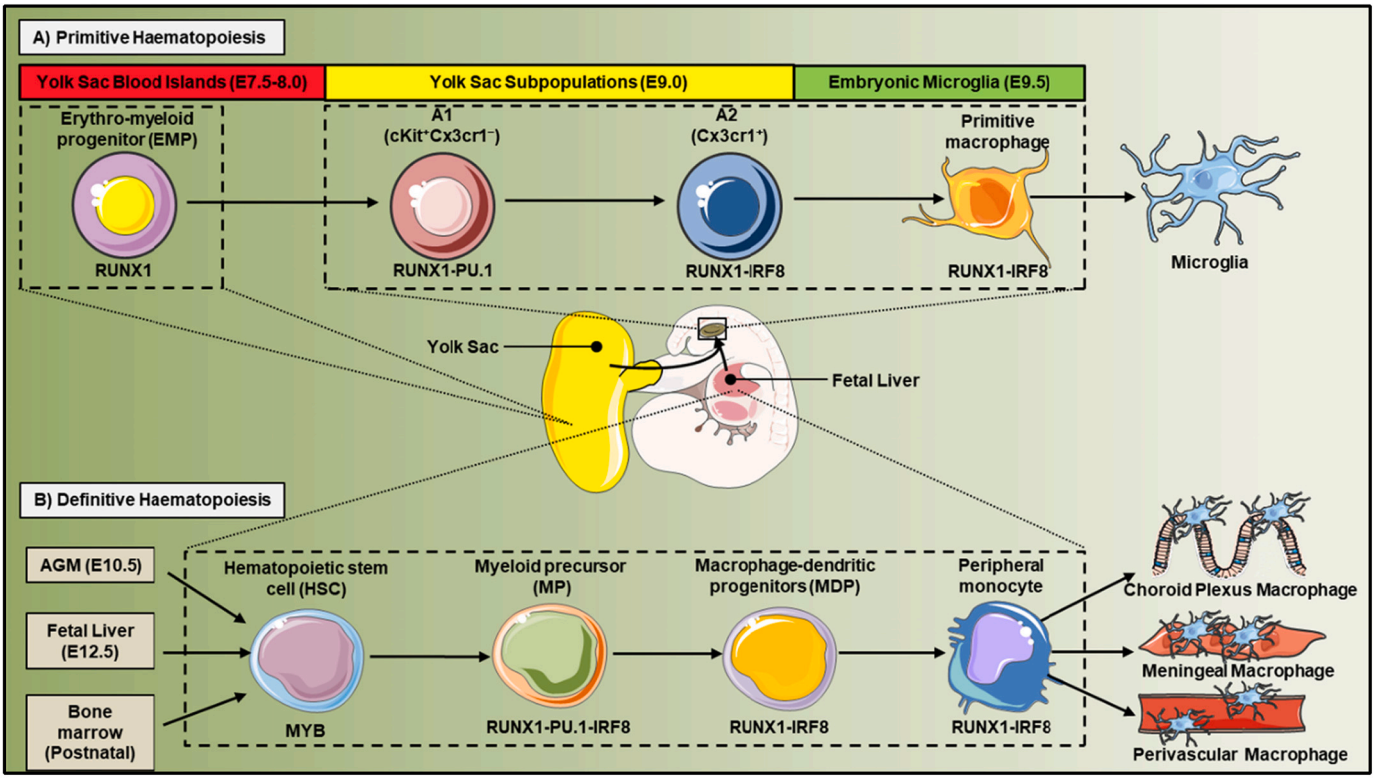

Fig. 1. This diagram illustrates the growth and development of microglia as well as other CNS macrophages. (A) A transitory initial phase of myeloid cell development is termed primitive haematopoiesis. It begins at E7.5-8.0 in the blood islands of the yolk sac and progresses to the formation of erythro-myeloid progenitors. These cells further evolve into A1 ($cKit^{+}Cx3cr1^{-}$) cells, preceded by A2 ($Cx3cr1^{+}$) cells, which ultimately transform into microglia. (B) Conversely, other CNS macrophages present in the meninges, choroid plexus and perivascular spaces are believed to be originated from definitive haematopoiesis, which begins at E10.5, first in AGM and then, at E12.5 in the fetal liver. Postnatally, hematopoiesis in the bone marrow forms monocytes. HSC produce monocytes from MPs and MDPs. EMP, erythro-myeloid progenitor; RUNX, runt-related transcription factor 1; PU.1, transcription factor PU.1; IRF8, interferon regulatory factor 8; AGM, aorta–gonad–mesonephros; HSC, haematopoietic stem cells; MYB, transcriptional activator MYB; MP, myeloid precursor; MDP, macrophage and/or dendritic cell progenitor.

invade tissues following infection or immune attack and they can rejuvenate populations of several tissue macrophages (Haldar and Murphy, 2014; Jenkins and Hume, 2014). In contrast to monocytes, CSF1 (colony stimulating factor 1) is another essential component in the development of microglial cells. CSF1, also referred to as MCSF (macrophage colony stimulating factor), supports macrophages by means of its tyrosine kinase receptor protein, CSF1R (colony stimulating factor 1 receptor), which is expressed on microglia, monocytes and macrophage precursors (Jenkins and Hume, 2014; Nandi et al., 2012). The osteopetrotic mouse effectively lacks the receptor, instigating a variety of skeletal and hematopoietic deformities, as well as a decrease in the levels of microglial cell populations ranging from 30% to a total depletion dependent on the location (Kondo et al., 2007; Wei et al., 2010b; Wiktor-Jedrzejczak et al., 1990). Although CSF1 may not be a ligand for the receptor; but, interleukin-34 (IL-34) is. And, in comparison to CSF1, IL-34 is much more abundant and frequently expressed, whereas their varying local expression constitutes the variance between CSF1 and CSF1R knockout phenotypes (Wei et al., 2010b). By using IL-34 deficient mice, it was shown that IL-34 is a significant factor for the differentiation of microglia population (Y. Wang et al., 2012). Adult mouse brains sustain elevated levels of IL-34 and CSF1, while CSF1R levels decline during the postnatal stage (H. Lin et al., 2008; Nandi et al., 2012). The primary conclusion of all these studies in rodents and humans is that microglial cells are produced from yolk sac macrophages, which triggers brain growth during the early fetal developmental phase.

2.2. The M1/M2 profile of microglia/macrophages

Microglia and macrophages are typically categorized into M1 and M2 phenotypes in order to evaluate whether they have anti-tumor or tumor-promoting characteristics. Ponomarev et al., first discovered the concept of microglia polarisation in murine rodents (Ponomarev et al., 2007). They revealed that the M2-associated protein CHIL3 (chitinase-like protein 3) was induced by microglia in an IL-4 dependent fashion (Ponomarev et al., 2007). Microglia exhibit M1/M2 polarization, which is identical to that seen in macrophages. Based on *in vitro* initiation state, macrophage polarization is allocated into classical pro-inflammatory (M1; responsible for Th1 responses, type I inflammation, destruction of intracellular pathogens) and alternative anti-inflammatory (M2). Alternative anti-inflammatory stimulation can be further divided into M2a (Th2 response, type II inflammation, allergy, destruction of pathogenic substances), M2b (Th2 stimulation, immunoregulation), and M2c (deposition of matrix, immunoregulation, tissue remodeling) activation (Mantovani et al., 2004; Fernando Oneissi Martinez et al., 2008). The M1 cells can instigate anti-tumorigenic responses via introducing antigen to adaptive immune cells, causing phagocytosis of tumorigenic cells and generating pro-inflammatory cytokines, whereas the concurrently stimulated pathway, M2, is differentiated by the expression of surface markers CD163 (cluster of differentiation 163) and CD204, as well as the expression of intracellular STAT3 (Signal transducer and activator of transcription 3) and the generation of arginase (Gabrusiewicz et al., 2011; Pollard, 2004). Polarization of M2 cells inhibits the formation of cytokines needed to aid tumor-specific $CD4^+$ T helper 1 (Th1), and $CD8^+$ T cells and facilitates the role of $CD4^+$ regulatory T cells, and hence promotes tumor support (Wei et al., 2010a; Zou et al., 1999). In GB, glioma cells may inhibit the M1-like microglia while inducing the M2-like anti-inflammatory microglia. Furthermore, employing two-color time-lapse fluorescence microscopy on brain samples from a rodent glioma model, researchers revealed that glioma cells can trigger the process of motility in microglial cells (Juliano et al., 2018). Research has shown that LPS (lipopolysaccharide) regulates the polarization of the M1/M2 microglia phenotype, based on the inflammatory reaction or tissue homeostasis (Lisi et al., 2014; Tanaka et al., 2015). An *in vitro* analysis by Halleskog et al., employing purified microglia and LPS-stimulated organotypic hippocampal slices shows that lithium chloride inhibits serine/threonine kinase GSK-3 (glycogen synthase kinase 3), repressing the M1 genes, like iNOS (inducible nitric oxide), IL-1β, IL-6, and TNF-α (tumor necrosis factor α), and microglia cells to the M2 genes, including IL-10 and MRC1 (mannose receptor 1) (Halleskog and Schulte, 2013). Glioma cells produce a variety of factors that impede immunological cells, like MIF (macrophage inhibitory factor), TGF-β (transforming growth factor β), PGE2 (prostaglandin E2), IL-4, IL-6, IL-10 and MCSF (Bach et al., 2009; Komohara et al., 2008; Qiu et al., 2011; L. Zhang et al., 2007). Many of these cytotoxic factors are reported to stimulate the M2-like phenotype and/or inhibit the M1-like phenotype. Microglia was shown to be polarized to an M2-like phenotype, for example by IL-4, IL-6, and IL-10 (Sica et al., 2006), while TGF inhibits proliferation of microglia and the development of pro-inflammatory cytokines *in vitro* (A. Wu et al., 2010). In addition, transcription of immune suppressive molecules like B7-H1 (B7 homolog 1) and immunosuppressive processes like dysregulation of ICAM-1 (intercellular adhesion molecule 1) may deteriorate the microglial T cells integrated immune sensing and removal of gliomas (Gomez and Kruse, 2006). M2-like GAMs (glioma-associated microglia/macrophages) also facilitate the development and survival of glioma by promoting angiogenesis and suppressing tumor apoptosis. GAMs were shown to produce growth factors like PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor) and members of the FGF (fibroblast growth factor) family, and an association was found between GAMs and tumor vascularity in gliomas (Nishie et al., 1999). GAMs are an important reservoir of FasL (Fas ligand) expression, which is likely to lead to the repression of glioma apoptosis (Badie et al., 2001). Additionally, it was discovered that ADCC (antibody-dependent cell mediated cytotoxicity) is involved in microglia anti-tumor processes. Sutter et al., demonstrated that microglia which were derived from the brain cortices of neonatal mice have been shown to annihilate human tumorigenic cell lines expressing diverse concentrations of EGFR (epidermal growth factor receptor) in the presence of a monoclonal antibody particular to EGFR (Sutter et al., 1991). As a result, for glioma patients, manipulation of core molecular targets and pathways that could alter the polarization states of the M1/M2 phenotype in microglia could be part of novel therapeutic tactics to destroy tumor cells, particularly in GB.

2.3. The M1/M2 continuum: Is it obsolete?

Amongst the most critical issues that should also be addressed is that the M1/M2 classification system is troublesome when concerned with microglia. The primary nomenclature for the M1/M2 system originated from macrophage studies, and much of the published research has simply interpreted this M1/M2 classification to microglia, with no clear distinctions between these two populations (Fernando O. Martinez and Gordon, 2014). For a variety of purposes, the use of M1/M2 as a classification is not permitted. To begin, much of the evidence supporting this classification comes from *in vitro* studies that have never been adequately replicated *in vivo* (Sousa et al., 2017). Such frameworks seldom transform into functional models because *in vitro* models have minimal interactions with significant systemic factors beyond cell adhesion, maturation, and cytokine release (Davies et al., 2013). Furthermore, macrophages *in vivo* and macrophages *in vitro* have different morphologies, behaviours, and expression profiles (Sousa et al., 2017). The M1/M2 phenotype terminology is also obsolete in the context that its original description predates the significant outbreak of recent genomics work that has arisen over the past 15 years. Genomic studies of both glioma-associated macrophages and microglia in the GL261 murine glioma model by Szulzewsky et al., (Szulzewsky et al., 2015) have demonstrated that both of these cell types have different expression profiles, which do not fall into any formerly reported M1/M2 system (Gabrusiewicz et al., 2016). Evidently, such myeloid populations were only marginally associated with previously identified M1/M2 phenotypes, with 59.6% of the genes that were substantially increased (261/438) are not classified as M1 or M2; this implies that there is much more ambiguity than the M1/M2 classification can offer, at best from a

genomic viewpoint (Szulzewsky et al., 2015). We have recently begun to understand the different variations exist between macrophages and microglial cells in respect of structural, functional, and expression of tumor-associated signaling mechanisms (Satoh, 2018; Szulzewsky et al., 2015). As a result, whereas the M1/M2 classification for macrophages has generalization issues, using this classification system for microglial cells could be problematic. Notably, a large number of genomic analyses of microglial cells were implemented in a number of disease models, together with glioblastoma (Müller et al., 2017), traumatic brain injury (Morganti et al., 2016), Alzheimer's disease (Efthymiou and Goate, 2017), and ALS (amyotrophic lateral sclerosis) (Sousa et al., 2017). However, none of the studies revealed conclusive evidence of a specific M1/M2 distinction between microglia, but rather that both M1 and M2 phenotypic features were expressed concurrently. Moreover, distinguishing microglia across the M1/M2 spectrum is difficult, particularly in GB, because active microglia profile in the tumor milieu plays a multitude of roles, which do not exclusively belong to the conventional functional classifications, consistent with the M1/M2 system in macrophages. For instance, even though the M2 phenotype for macrophages is primarily considered as immunosuppressive – particularly in the case of elevated trophic polyamines – the M2 subset in microglial cells may probably play a relatively intense pro-tumorigenic function that promotes formation, development and invasion of gliomas (Italiani and Boraschi, 2014; Orihuela et al., 2016; S. Y. Wu and Watabe, 2017; Yamasaki et al., 2014). Since such cancer-specific associations either with microglia or macrophages exists, we need to specifically delineate between the two to avoid constructing confusing experimental protocols. Besides that, we must exercise caution when solely adhering to the M1/M2 system for microglia and macrophages, since they are diverse and have numerous variations with one another, rendering this altered classification system largely erroneous. Lastly, examining the discrepancies between macrophages and microglia might give us an overview of GB progression, resistance to targeted therapies, and potential strategies toward novel therapeutic treatments.

2.4. Role of microglia in development

A large number of studies have revealed that microglia plays an important function in developmental processes (Bilimoria and Stevens, 2015; Derecki et al., 2014; Filiano et al., 2015; Michell-Robinson et al., 2015). Within the CNS, the surrounding parenchyma is consistently scanned by microglial cells to detect any alterations in brain activity (Davalos et al., 2005; Nimmerjahn et al., 2005). And they are also involved in the regulation of neurogenesis, neuronal excitability, synapse activity, and apoptotic cell clearance throughout the healthy adult brain (Lenz and McCarthy, 2015). Microglia interacts with the cerebral microenvironment thru a variety of molecules, including cytokines, chemokines, and neurotrophic factors that further modulate microglial actions by transforming homeostatic microglia into an active microglia (Q. Li and Barres, 2018) and promoting tip-cell fusion in order to participate in angiogenesis (Deczkowska et al., 2018; Fantin et al., 2010). Microglial cells are highly-trained phagocytes of the brain and eradicate entire cells or cellular sub-structures, especially synapses. Microglial cells identify cells that undergo apoptosis, and they move to distinctive regions of the CNS, typically either before or during the peak of the programmed cell death period. In an *in vivo* study, Nimmerjahn et al. showed that in normal adult brains, microglia are constantly active and continually surveying their surrounding microenvironment with particularly motile processes and protrusions, and are often referred to as *"sentinels"* (Nimmerjahn et al., 2005). Hanish and Kettenmann, however, fortified this novel understanding of microglia as vigorously active and robust, swapping the theory of resting vs. activated microglia. In addition, it was stated that microglia activation relies on pathological insult, and that microglial cells are highly dynamic in nature because of their adaptation to micro-environmental changes (Hanisch and Kettenmann, 2007). One well-known and most critical process during the development phase is synapse pruning, referring to the eradication of extra synaptic connections. Microglia-synapse connections are very important during the growth and developmental phase. CX3CR1 (C-X3-C motif chemokine receptor 1) is expressed by microglia while its ligand, fracktalkine, also known as CX3CL1 (C-X3-C motif chemokine ligand 1), can either be released from neurons or located on the surface of the cells and aids in the establishment of a connection between neurons and microglia in the CNS (Gundra et al., 2014; Hughes et al., 2002; Jung et al., 2000). Microglia are the only intrinsic brain cells that express receptors for fractalkine CX3CR1. In a study, Paolicelli et al., revealed that CX3CR1 knockout mice had intermittent synapse pruning deficiencies, which is consistent with single-cell recordings of CA1 pyramidal neurons showing a reduced spontaneous excitatory postsynaptic current/miniature excitatory postsynaptic current (EPSC/mEPSC) amplitude ratio, reflecting immature connection (Paolicelli et al., 2011). CX3CR1-deficient mice showed decreased connectivity between the cortex and hippocampus, which also had an impact on mouse behavior, learning and network grid development (Fillman et al., 2013; Rogers et al., 2011; Voineagu et al., 2011). In addition, it has recently been determined that the transiently active microglia subpopulation found in the early postnatal white matter area would promptly lead to the preservation of oligodendrocyte progenitor populations and consequent myelinogenesis in the mouse, because a declined oligodendrocyte progenitor population was observed after the insertion of selective CSF-1R inhibitor BLZ945 that significantly decreases microglia populations (Hagemeyer et al., 2017).

3. Microglia and glioblastoma

3.1. The role of microglia in glioblastoma malignancy

It has been hypothesized that the immune and glial cells may not perceive cancerous cells as some foreign invaders, so therefore do not destroy them, but rather assist them in infiltrating the surrounding tissues (Roggendorf et al., 1996; Z. M. Zhang et al., 2015). In general, depending on the various environmental settings and stimulatory factors, microglia may be rapidly stimulated through a variety of molecular and cellular mechanistic processes, subsequently converted into an active state, and help to strengthen toll-like receptors (TLRs) expression, which promptly binds microbial complexes (Arcuri et al., 2017b). Despite the fact that microglial cells are vital to repair CNS injuries in normal settings, activated microglia represses brain repair activities via blocking the segregation of oligodendrocyte precursors into myelinating oligodendrocytes by utilizing different mechanistic processes like generation of heat shock protein (HSP) 60, NO-dependent oxidative damage and TNF-α signaling (Y. Li et al., 2017; Pang et al., 2010). Excessive stimulation of microglial cells may cause mitochondrial dysfunction and greatly reduce the consumption rates of oxygen in mitochondria, depending on the extent of their functional activities, affecting the overall brain metabolism rate and worsening clinical status (Ghosh et al., 2018). Moreover, excessively-stimulated microglial cells ensure detrimental consequences on neurogenesis, exacerbating long-term neural deficits by impeding the axonal regeneration mechanism, which ultimately leads to neuronal death (Papageorgiou et al., 2016; Rodríguez et al., 2017). Microglial cells assist GBs by contributing to tumor development via secreting copious amounts of anti-inflammatory and pro-tumoral factors, like EGF (epidermal growth factor), STI-1 (stress-inducible protein 1), IL-6, IL-1β, TGF-β and MT1-MMP (membrane type 1-matrix metalloproteinase) (Carvalho Da Fonseca and Badie, 2013; Coniglio et al., 2012; Markovic et al., 2009). Recently, Liddelow et al. demonstrated that microglial cell activation serves an important role in the induction of neurotoxic reactive astrocytes through the production of IL-1α, TNF, and C1q (complement component 1q). Reactive astrocytes triggered via active microglia, named A1, gradually forfeit their homeostatic properties, resulting in the death of differentiated oligodendrocytes and neurons (Liddelow et al., 2017). Another

study found that activated microglia inhibit anti-inflammatory TGF-β signaling through the downregulation of TGF-β mediated gene expression, which exacerbates severe microglial dysregulation, partially via the NF-κB (nuclear factor-kappa B) pathway (Affram et al., 2017). A significant number of studies have discovered that higher degree of GAM infiltration contributes to tumorigenesis by fostering immune suppressive environments and invasive characteristics (Carvalho Da Fonseca and Badie, 2013; Anna Carolina Carvalho Da Fonseca et al., 2016).

3.2. Factors involved in the interplay between microglia and glioblastoma

A variety of chemotactic factors triggered and released via tumorigenic cells recruit microglia at the tumor site (Arcuri et al., 2017a; Russo et al., 2016). Among them, the most important ones are cytokines, chemokines, metabolic, neurotrophic and morphogenic factors, as well as extracellular matrix components (Fig. 2) (Matias et al., 2018).

3.2.1. Cytokines

Cytokines are a group of small molecular compounds with varying activities which depend on their micro-environmental settings. They are comprised of polypeptides and glycoproteins that put forth anti-inflammatory, pro-inflammatory or immune suppressive effects. Cytokines released by glioblastoma cells exhibit extensive impacts, involving tumor proliferation, migration, invasion, and angiogenesis (V. F. Zhu et al., 2012). Cytokines can be classified into the following categories: interleukins (ILs), growth factors, colony-stimulating factors, IFN (α, β, and γ), TNF, and chemokines. Based on the underlying microenvironment, these different cytokines may have pro- and anti-inflammatory, or immunosuppressive consequences (Iwami et al., 2011). Among cytokines most frequently found to be exceedingly expressed in tumorigenic cells are TGF- β, TNF-α, IL1-β, IL-6, IL-8, IL-10, IFN-γ, GM-CSF (granulocyte–macrophage colony-stimulating factor), VEGF and CX3CL1.

3.2.1.1. Transforming growth factor–β. Transforming growth factor-β (TGF-β) is one of the best described cytokines in GB. Depending on the intensity of tumorigenesis, TGF-β plays multiple and dynamic roles in the growth and development of cancer (Landskron et al., 2014). TGF-β isoform has three receptors that trigger the activity of downstream genes, including VEGF to accelerate migration, invasion and angiogenesis of tumorigenic cells (Di et al., 2012). TGF-β proteins are not typically constructed in the brain. However, they were found to be highly expressed in glioma (V. F. Zhu et al., 2012). In the initial phases of tumorigenesis, TGF-β acts as a strong inhibitor of astrocytes, immune and epithelial cell growth by enhancing apoptotic cell death and hampering the progression of the cell-cycle (Joseph et al., 2013; Landskron et al., 2014). But, in advanced stages, TGF-β tends to increase tumor invasion as well as metastasis via invading the glial mesenchymal transition (Morrison et al., 2013). In addition, increased TGF-β2 levels are also correlated with advanced disease stages and cause immunodeficiency in individuals with gliomas (Kjellman et al., 2000). Studies exhibited that microglial cells secrete TGF-β, and its inhibition abrogates glioma growth (Wesolowska et al., 2008). Zhu et al., recently showed that the TGF-β levels were 2-fold greater in microglia cultured with glioma-conditioned medium (G/MCM) relative to glioma-conditioned medium (G/CM), meaning that the glioma environment accelerates the production of TGF-β levels in microglia (W. Zhu et al., 2016).

3.2.1.2. Interleukins. The workings of the immune system is heavily reliant on ILs, specifically for the development and differentiation of different cells, including B-cells, T-cells and hematopoietic cells (Benveniste, 2014). ILs also act as a significant player in various types of

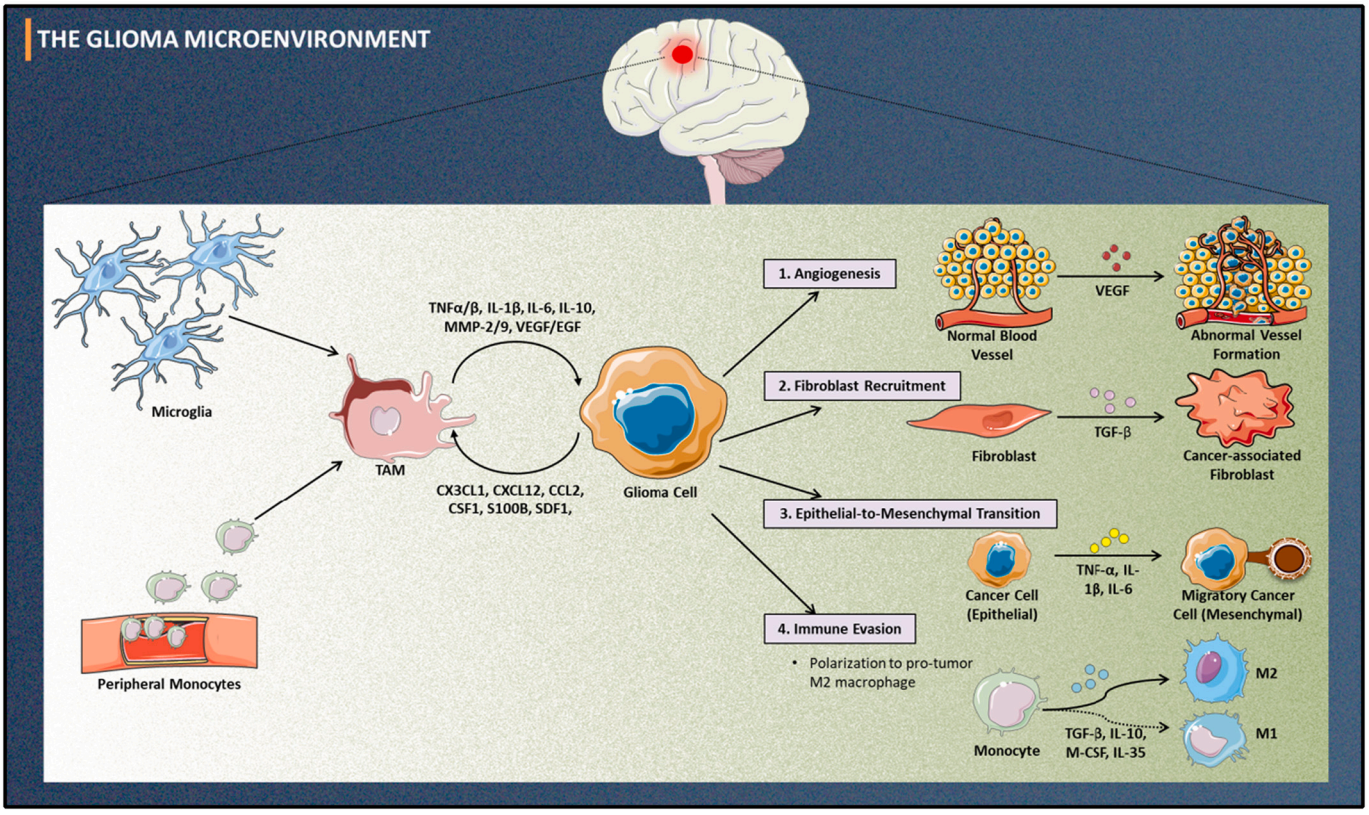

Fig. 2. A graphical illustration of the glioma microenvironment. The glioma microenvironment consists of several cellular components around the tumour mass, such as immune cells, fibroblasts, and epithelial cells, as well as acellular components like extracellular matrix and blood vessels. Glioma cells exude molecules that influence the tumour microenvironment and contribute to GB development via immune evasion, metastatic niche formation, neo-angiogenesis, and many others.

cancers, including glioblastoma. Currently, there are 36 different types of ILs. However, IL-1β, IL-6, IL-8 and IL-10 are found in close proximity to malignant cells to facilitate carcinogenesis by activating proliferative mechanisms and/or activating numerous signaling cascades involved in proliferation, invasiveness, migration and angiogenesis. Interleukins are potent stimulator of several signaling pathways that help regulate cell survival and facilitate chemotherapy resistance. Hence, targeting of these inflammatory cytokines in the GB microenvironment may offer therapeutic benefits to individuals with GB (Yeung et al., 2013). IL-10 is a pivotal interleukin that regulates important immunological responses in several brain regions (Lobo-Silva et al., 2016). IL-10 is formed by a variety of cells, including glioma cancer stem cells (gCSCs). It has been discovered that IL-10 inhibits the development of a variety of cytotoxic factors via Th1 cell repression and promotes the advancement of glioma (Carlsson et al., 2010). *In situ* hybridization tests revealed that both astrocytes and microglia promote the expression of IL-10 in GB (Huettner et al., 1997). The primary cells from glioma specimens have revealed that macrophages and/or microglia are indeed the key elements of IL-10 induction in GB conditions (Wagner et al., 1999). This indicates that GB cells inhibit the immune responses by IL-10, which has the ability to suppress the expression of major histocompatibility complex class II (MHCII) molecules in microglia, thus impeding T-cell proliferation (K Frei et al., 1994). Thus, in this sense, IL-10 downregulates the production of several pro-inflammatory cytotoxic factors in GAMs, for example TNF and IFNs (Fulton et al., 1998). IL-10, in conjunction with IL-4, IL-13, and glucocorticoid hormones, stimulates the activity of GAMs to attain M2-like phenotypic characteristics (Mantovani et al., 2002). In a study, Cai et al. recognized six different cytotoxic signals in a population of glioma individuals with low mortality rates. Besides that, researchers linked these cytotoxic factors with the M2-like phenotype, like elevated levels of mRNA expressing TGF-β1 and IL-10, with glioma progression (Cai et al., 2015).

Another interleukin that is highly up-regulated in glioblastoma is IL-6 (Tchirkov et al., 2001). IL-6, together with its receptor, is found to be strongly expressed in both GB tumors as well as GB cell lines (Hao et al., 2002; Samaras et al., 2009). IL-6 is released by several cells, for example neurons, microglia, astrocytes, and peripheral monocytes (Samaras et al., 2009). Because of its role in GB development, expression levels of IL-6 were found to be inversely correlated with glioma longevity (Tchirkov et al., 2001). The expression level of IL-6 in GB is higher compared to the normal brain and the level of RNA expression of IL-6 relates with GB pathology. CCL2, produced by tumor cells, has been shown to upsurge the levels of IL-6 release through microglial cells, which are linked with growth and invasiveness of GB in a TLR4-dependent fashion (Hamilton, 2008; Sielska et al., 2013). During tumorigenic infiltration, IL-6 produced by microglial cells raises the expression of MMP-9 (Yeung et al., 2013). Furthermore, a recent study discovered that microglia are indeed not the only glial cells in the brain that express IL-6; astrocytes also express increased concentrations of IL-6 specifically in GB, which causes glioma cells to migrate and invade by expressing an activated form of MMP-14 (W. Chen et al., 2016).

3.2.2. Chemokines

Chemokines are a class of cytokines that have chemotaxis properties and are members of the cytokine family. Chemokines facilitate various functions such as proliferation, activation, and trafficking of cells by binding to GPCRs (G-coupled protein receptors). Chemokines are expressed abundantly via microglia and are particularly crucial for their induction and instigation in various cancers (Sciumè et al., 2010). Chemokines, such as CX3CL1/CX3CR1, CXCL12, CXCL12/CXCR4, CXCL16/CXCR6, CXCR7, CCL2/CCR2, and CCL5/CCR5, are found of prime significance in tumor growth (Dzaye et al., 2016; Hattermann et al., 2014; Laudati et al., 2017). GB exhibits a significant amount of mRNA and protein expressions of CX3CL1 (Held-Feindt et al., 2010; Park et al., 2012). Expression of CX3CR1 was found to be lacking in tumorigenic cells; however, it was shown to be expressed in microglial cells itself that lack CX3CL1 expression (Held-Feindt et al., 2010). CX3CL1 stimulates macrophages and microglial cells by acting as a chemoattractant. The CX3CL1 released by glioma cells stimulates the recruitment of GAMs via CX3CR1 and enhances the concentration of various MMPs (2, 9, and 14) in GAMs, promoting tumor infiltration (Carvalho Da Fonseca and Badie, 2013; Held-Feindt et al., 2010) In GB patients, the CX3CR1 gene has been linked to a relatively high survival percentage and lessened microglia infiltration rates (Rodero et al., 2008). CXCL12 is also expressed ubiquitously in healthy as well as GB individuals (Goffart et al., 2017). The murine astrocytoma cell line, ALTS1C1, a new glioma model, released significantly higher levels of CXCL12 *in vivo* and *in vitro*. In a study, Wang et al., have shown that CXCL12 inhibition with a particular siRNA (small interfering RNA) has decreased tumor invasion and constructed tumors have a defined set of boundaries. They also discovered that inhibiting CXCL12 synthesis decreased GAM migration to hypoxic regions. A number of brain tumor studies have shown that inhibition of CXCL12/CXCR4 axis by using an antagonists inhibits the development, angiogenesis, and recurrence of tumor cells, indicating that this practice may be a viable therapeutic alternative for glioblastoma (Guo et al., 2016; Nervi et al., 2009). The monocyte chemoattractant protein-1 (MCP-1/CCL2) is also thought to play a role in the recruitment of macrophages and/or microglia to gliomas (Deshmane et al., 2009; Leung et al., 1997; Platten et al., 2003; Ueno et al., 2000). MCP-1, produced by tumorigenic cells, binds to CCR2, on the microglial cells, allowing more microglial cells to be recruited at the tumor site (Galasso et al., 2000). Kuratsu et al., reported that MCP-1 expression is positively associated with the higher level of gliomas, meaning that the expression of MCP-1 in glioma cells not just causes the induction of microglia but also fosters tumor growth and development (Kuratsu et al., 1993). Furthermore, it was reported that the expression of CCR5 and CCL5 has also been linked with shorter overall survival rate and poor prognosis of glioblastoma patients (Laudati et al., 2017). According to a study by Pan et al., CCL5 released by glioma cells increases cell survival rate by exploiting CD44 as a receptor, to inhibit apoptosis (Pan et al., 2017). Another research discovered that the CCR5 inhibitor, maraviroc, decreased the concentrations and activities of M2-like markers arginase 1 and IL-10. In addition, CCR5 inhibition was associated with a substantial decrease in microglial cell migration, which was triggered by PI3/AKT inhibition (Laudati et al., 2017). CXCR3 is a receptor for CXCL9, CXCL10 and CXCL11. Both CXCR3 and CXCL11 are abundantly expressed in high grade gliomas, and the receptor is significantly linked with the advancement of glioma. In an animal model, its antagonist (NBI-7433), was shown to suppress the progression of tumor cells and extend the overall survival time (V. F. Zhu et al., 2012). This represents that cytokines and chemokines are crucial factors involved in microglia-glioblastoma interplay. Investigating their roles in gliomagenesis, migration, and invasion may offer explanations for metastatic mechanism as well as other malignant mechanisms in GB.

3.2.3. Glial cell-derived neurotrophic factor

GDNF (glial cell-derived neurotrophic factor) is an important survival component which belongs to the TGF protein family and governs a multitude of neural functions. GDNF was first discovered as a trophic factor required for the maintenance of dopaminergic neurons in the nigrostriatal pathway and is now a well-established clinical target in Parkinson's disease (Airaksinen and Saarma, 2002; L. F. H. Lin et al., 1993; Sariola and Saarma, 2003). GDNF, however, was eventually discovered to be strongly expressed in glioma cells, and was found as a significant proliferative component associated with glioma progression and migration (Fielder et al., 2018; Wiesenhofer et al., 2000b). Lin et al., isolated GDNF for the first time in B49 rat glial cell lines (L. H. Lin et al., 1994); it has since been confirmed to be strongly expressed in high-grade glioma cell lines (U251, C6 and U87) and tissues (Verity et al., 1999; Wiesenhofer et al., 2000a; B. Le Zhang et al., 2016). GDNF secreted from glioblastoma cells is a significant neurotrophic factor for a

range of neural populations, and it also acts as a strong chemotactic factor for microglial cells (Ku et al., 2013; Wiesenhofer et al., 2000b). Microglial cells have been shown to express GDNF receptors, specifically GFRa-1 and GFRa-2 (Honda et al., 1999; Rickert et al., 2014). Ku et al., reported that downregulation of GDNF via siRNA in mice xenografts of gliomas was shown to reduce the recruitment of microglial cells and generate smaller tumors. However, their results also revealed that overexpression and downregulation of GDNF does not affect the astrogliosis mechanism (Ku et al., 2013).

3.2.4. Metabolic factors

Every single cell in our body, including microglial cells, requires a huge amount of ATP to function (Davalos et al., 2005; Jackson and Robinson, 2018). Studies have reported that the metabolic alterations occurring in microglial cells are crucial for understanding the M1–M2 phenotype polarization phase that occurs in GB condition (Ghosh et al., 2018; Orihuela et al., 2016). According to Orihuela et al., disruptions in mitochondrial respiration and metabolic circuitries occur during the polarisation phase of M1 and M2 phenotypes in microglia (Orihuela et al., 2016). Rudimentary metabolites like those of glucose, glutamine, and fatty acids are transported by a variety of transporters in microglial cells (Ghosh et al., 2018). It was reported that the family of glucose transporters (GLUTs) are essential proteins, which influence the distribution of glucose molecules in microglial cells as well as in tumors (B. Le Zhang et al., 2016). Moreover, GAMs were found to release GLUT5 in non-necrotic regions of the tumor (B. Le Zhang et al., 2016). A study demonstrated that microglia increases the secretion of IL-6 under glucose deprivation (GD) conditions (J. Choi et al., 2015) and also their phagocytosis activities (Churchward et al., 2018). Such findings suggest that IL-6 and phagocytic activities are linked with the M1 phenotype in microglial cells. Hambardzumyan et al., have demonstrated that lowering glucose concentration in GB or suppressing GLUT5 could be an effective way to provoke M1 polarization state in microglia and, as a result, decrease the aggressive nature of tumor cells (Hambardzumyan et al., 2015b). Furthermore, in GB, the presence of mutations, particularly in cellular enzymes like IDH (isocitrate dehydrogenase), has been linked to improved survival and prognosis rate when compared to IDH wild-type (Louis et al., 2016). In general, IDH1 restricts the catalysis of isocitrate into α-ketoglutarate (α-KG) to generate NADPH (nicotinamide adenine dinucleotide phosphate) from $NADP^+$. On the other hand, IDH2 regulates the opposite reaction, causing conversion of α-KG into isocitrate in mitochondria (Al-Khallaf, 2017). During the occurrence of mutation, including IDH1-R132 and IDH2-R172, causes a reduction in α-KG and an upsurge in R-2-hydroxyglutarate (2HG), an oncometabolite that triggers changes in histone methylation and chromatin complexes (Amankulor et al., 2017; Ward et al., 2010). Zheng et al. performed a cohort study on 60 individuals with the IDH1–R132H mutation in GB to determine whether the IDH1–R132H mutation was present in the GAM populations. According to their results, the IDH1–R132H mutation was found in a population of $CD68^+$, $IBA1^+$, and $CX3CR1^+$ GAM individuals (Zheng et al., 2012). Additionally, rodents with the IDH1–R132H mutation had higher concentrations of DNA methylation and 2-HG, in addition to limited immunoregulatory properties, for instance, significantly lower microglial cells (Amankulor et al., 2017; X. Zhang et al., 2016). Turcan et al. revealed that IDH-type alterations in cancer victims may have a chance of higher survival and better prognosis rate (Turcan et al., 2012). As a result, IDH has the ability to be a therapeutic target for reducing the intensity of GB cells by regulating microglial activities.

3.2.5. Extracellular matrix proteins

The extracellular matrix (ECM) consists of hundreds of different molecules that interact in a complex and tightly ordered manner. The constituents of ECM interact with one another and such interactions amongst cells and matrix are critical for the healthy functioning of the tissues. ECM plays a vital role in survival, maturation, migration, cell fate, tissue homeostasis and invasion (Frantz et al., 2010; Lu et al., 2012). But the aberrant release of ECM proteins in brain tumors, including GB, triggers significant alterations in brain tissues (Rao, 2003). Yeh et al. studied the characteristics of ECM proteins in GB growth and reported that matrix secreted primarily via GB cells could influence the properties of microglial cells to release several pro-invasive components (Yeh et al., 2012). They also discovered that the rat C6 astrocytoma cell line generates higher concentrations of ECM proteins including fibronectin and vitronectin that are either inactive or present at lower concentrations in healthy astrocytes (Yeh et al., 2012). Farber et al., demonstrated targeting GB in a mouse model with an inhibitor of α5β1 integrin, a fibronectin receptor, inhibited aggregation of GAMs at the tumor site and halted the incursion of tumor cells into neighboring parenchymal regions (Färber et al., 2008). It has been shown that α5β1 integrin is expressed on both glioma and microglial cells, so interfering with it could influence the activity of both of these cells. However, the detailed mechanism by which fibronectin binds with GSCs (glioma stem cells) as well as the associated molecular frameworks remain unknown. Gong et al., recently discovered that miRNA-1271 limits the proliferation of neuroglioma cells by targeting fibronectin 1 (J. Gong et al., 2017). Several other reports have shown that fibronectin promotes cell adhesion-mediated resistance to drugs in a variety of different tumors (Fei et al., 2013; Hazlehurst et al., 2006; Nakagawa et al., 2014). Osteopontin (OPN), a secreted glycoprotein that can bind to integrins and CD44, has been linked to increased invasion and metastasis in a number of cancers, including GB (Atai et al., 2011). Glioma cell lines stimulated with OPN have increased motility and intrusive properties (Jan et al., 2010; Yan et al., 2010). This indicates that osteopontin is a highly specialized ECM protein released by GAMs to promote glioma cell infiltration. Another important extracellular matrix glycoprotein is tenascin-C (TNC), a non-filamentous protein that regulates cell-cell and cell-matrix interactions. During normal embryonic development, TNC is abundantly expressed and contributes to embryogenesis and morphogenesis (Jones and Jones, 2000). TNC can associate with a variety of cell receptors, most notably integrins and EGFR. And is abundantly expressed and associated with tumor malignancy, as well as with poor glioma outcome (Leins et al., 2003). In a study, Bourdon et al. demonstrated high levels of TNC in GB using the monoclonal antibody (MAb) 81C6. They reported that antibodies that restrict TNC interactions reduce the motility of differentiated gliomas in culture and inhibit glioma growth in mice (Bourdon et al., 1983). Other studies subsequently confirmed this finding (Castellani et al., 1995; Hasegawa et al., 1997; Jallo et al., 1997; Natali et al., 1991; Zagzag et al., 1995). Fan et al., contrasted the cell surface glycoproteins of GSCs and typical adherent GB cells (U373 and U87) grown in serum-containing media and inferred that TNC is one of the five specific surface biomarkers for GSCs (He et al., 2010; Nie et al., 2015). In brain tumors, knockdown of TNC affects not just the migratory and invasive properties, but also the proliferative properties of tumorigenic cells. Though this result varied considerably from what was found *in vitro* (Xia et al., 2016) and also differed from the research of TNC evaluations in LN229, where reduction of TNC had no effect on tumor volume (Hirata et al., 2009). Moreover, Xia et al. discovered that TNC knockdown xenografts had a much more active microglial profile (Xia et al., 2016). Nonetheless, the neurobiological impact of activated microglial cells on tumorigenesis in TNC knockdown models requires further comprehensive research.

3.3. Effects of microglia on glioma stem cells

GBs are a type of cell that has stem cell-like characteristics, such as self-regeneration and multi-lineage differentiation, and are able to regenerate the local tumor after being incorporated into naive host cells. GSCs have phenotypic characteristics identical to healthy stem cells, may release CD133, and have the potential to self-renew themselves (Bao et al., 2006). Microglia and/or macrophages are found in and

around the perivascular niche of GSCs, implying that inflammatory mediators and cells are essential constituents for growth and development of GSCs. GSC-secreted chemoattractant agents drive microglia to the tumor mass, as well as the activated microglia produce several proteins that assist in GSC transformation and propagation by building a positive tumor environment (Lorger and Felding-Habermann, 2010). GSCs expressed up to three times more CCL2, CCL5, and CCL7, seven times more VEGF, and nearly fifty times more neurotensin than non-GSC glioma cells. Among these, neurotensin enhances the migration potential of microglia (Martin et al., 2005). And VEGF can stimulate the propagation of microglia while restricting myeloid progenitor maturation, resulting in the development of tumor-associated microglia and macrophages (TAMs), which facilitates the tumor progression (Forstreuter et al., 2002; B. Johnson et al., 2009). When xenografted into nude mice, GSCs mimic the initial polyclonal tumors and help facilitate radiation and chemotherapeutic resistance, contributing to progression and recurrence of tumorigenic cells (Bao et al., 2006; Hambardzumyan et al., 2006). A positive association between GSC and TAM suggests that GSCs can enlist TAMs aggressively than their more distinct neoplastic counterparts, highlighting the significance of GSCs in microglia recruitment. GSCs were found to be more effective at recruiting TAMs than glioma cell lines, suggesting that GSCs perform a prominent role in macrophage and microglia tropism to glioma (Yi et al., 2011). According to a report by Zhou et al., GSCs generate periostin, which accrues in the perivascular niche. Via the induction of integrin αvβ3 receptor signaling, periostin functions as a chemoattractant factor to recruit TAMs (Zhou et al., 2015). Inhibition of integrin αvβ3 signal activation by blocking peptides decreases macrophage recruitment and represses GSC infiltration (Feng et al., 2015). It has also been found that the periostin-integrin αvβ3 signal maintains the microglia and/or macrophages M2 phenotype, which ultimately contributes to the development of GSCs in brain tumors (Feng et al., 2015). Another mechanistic study conducted by Zong et al., reported that TGFβ1 expressed by TAMs abetted MMP-9 expression by GSCs. Conversely, TGFBR2 (transforming growth factor beta receptor 2) knockdown decreased the invasive properties of these cells *in vivo* (Ye et al., 2012). IL-6 was also recognized as a potential growth factor for GSCs, implying that IL-6 produced by microglia can facilitate development of GSCs (H. Wang et al., 2009). Moreover, Sarkar et al., have discovered that naive microglial cells disrupt the propensity of GSCs to infiltrate. Isolated microglial cells from non-glioma individuals expressed IL-8 and MCP-1 (monocyte chemoattractant protein-1), which suppressed the growth of glioma by restricting the capacity of GSCs to form clusters, while isolated microglia or monocytes cultured from glioma individuals do not have this anti-tumorigenic potential (Sarkar et al., 2014). Supplementation of GSCs with naive microglia-conditioned environment triggered growth arrest, decreased progression of GSCs, and significantly downregulated the growth and differentiation-related genes in GSCs. All these findings suggest that interaction between GSCs and microglia and/or macrophages promotes GSC invasion and proliferation properties.

4. Molecular signaling pathways of glioblastoma

4.1. *WNT signaling pathway*

The Wingless/Int1 (Wnt) signaling plays an important role in various stages of CNS development (Inestrosa and Arenas, 2010; Moon et al., 2004). The Wnt signaling pathway can be broadly classified into two different pathways: the canonical (β-catenin dependent) and the non-canonical (β-catenin independent) (Fig. 3), both of which are needed for various cellular and molecular processes (Barker and Clevers, 2006). In both adult and embryonic tissues, the canonical pathway is active in the development and preservation of stem/progenitor reservoirs, plus lineage determination (Grigoryan et al., 2008). The non-canonical Wnt mechanism, on the other hand, is a core modulator of cell mobility and tissue polarity, regulating not just heterogeneous extension activities in the course of gastrulation but also epithelial and neuronal migratory activities (Semenov et al., 2007). The Wnt/β-catenin pathway is abnormally programmed in GB pathogenesis due to the presence of multiple mutations and/or dysregulation of several proteins and enzymes (Lee, 2016). These alterations influence the signals conveyed across different cells, regulating a variety of responses, including inflammation (Kahlert et al., 2012; Kaur et al., 2013; C. Liu et al., 2011). It was hypothesized that Wnt components may also regulate microglia and glioblastoma interplay (Matias et al., 2019). Studies have shown that the Wnt proteins like Wnt3a and Wnt5a, expressed by cell bodies from the microenvironment are able to promote the recurrent stimulation of Wnt signaling in GB cells, thus increasing the concentration of Wnt in these cells (Götze et al., 2010; Halleskog et al., 2012). The Wnt/β-catenin signaling is also associated with the formation and development of gliomas, as well as survival of GSCs. Increasing evidence indicated that both canonical and non-canonical Wnt pathways perform an important role in the progression and maintenance of GSCs (Brennan et al., 2009; A. Gong and Huang, 2012; Lee, 2016). The glioblastoma Wnt-secreting cells and other adjacent cells like microglia that secrete Wnt proteins, may also lead to GB stemness, primarily thru the canonical pathway, and could also increase its invasive and aggressive properties, typically via the non-canonical pathway (A. Gong and Huang, 2012; Lee, 2016). Both microglia and astroglia express high levels of Wnt and FZD (frizzled) receptors, which play a significant role in regulating cellular and inflammatory activities like cell proliferation, migration, and invasion. Halleskog et al., discovered that a microglia cell line (N13 cells) and primary murine microglia express multiple Wnt receptors, including FZD4, 5, 7, and 8, as well as their co-receptors LRP5/6 (low-density lipoprotein receptor 5/6), which are sensitive to Wnt3a. They found no variations among N13 and primary microglia that have been associated with LRP and FZS receptors (Halleskog et al., 2011). According to two recent reports, Wnt5a, a non-canonical Wnt ligand, seems to be a key modulator of intrusive activities of GSCs *in vivo* (Binda et al., 2017; Hu et al., 2016). Binda et al. used *in vitro* invasion assay tests, gene expression analyses, and orthotopic xenograft mouse models of human gliomas to demonstrate that upregulated concentrations of Wnt5a govern the intrusive properties of patient-derived GSCs (Binda et al., 2017). From The Cancer Genome Atlas (TCGA) dataset, they determined that the mesenchymal subtype of GB expresses more Wnt5a than the classical and pro-neural GB signature profiles. Furthermore, the glioma groups with elevated Wnt5a expression displayed increased concentrations of CX3CR1 (CX3C chemokine receptor 1), CD163 (Cluster of Differentiation 163), connexin 43 (CX43), and IBA-1 (Ionized calcium-binding adapter molecule 1) (Dijksterhuis et al., 2015). The Wnt inhibiting factor 1 (WIF1) gene encodes a secreted Wnt antagonist that binds to Wnt proteins and sequesters them (Kawano and Kypta, 2003). The association of WIF1 with Wnt ligands specifically inhibits their binding with the cell surface cognate receptor down-regulating the stimulation of the Wnt pathway (Lambiv et al., 2011). In GB, WIF1 is downregulated resulting in the loss of WIF1 expression that may aberrantly activate Wnt signaling. Silencing of WIF1 expression is generally mediated by promoter hypermethylation, genomic deletion or both. This confirms that WIF1 is a candidate GB tumor suppressor gene. Lambiv et al. showed that forced WIF1 expression substantially lowered Wnt signaling in GB cell lines. This pattern was mirrored by a WIF1 dose-dependent amplification of cell proliferation *in vitro* and was associated with the total eradication of tumorigenicity (Lambiv et al., 2011). Nevertheless, the highly malignant GB cell line U87 escaped the effect either by blocking the ectopic expression of WIF1 or by becoming resistant to WIF1 expression.

4.2. *TGF-β signaling pathway*

TGF-β is a pleiotropic cytokine that regulates proliferation, differentiation, migration, invasion and tissue homeostasis (Fig. 4) (Verrecchia and Mauviel, 2002). There are three TGF-β isoforms, TGF-β1, 2 and

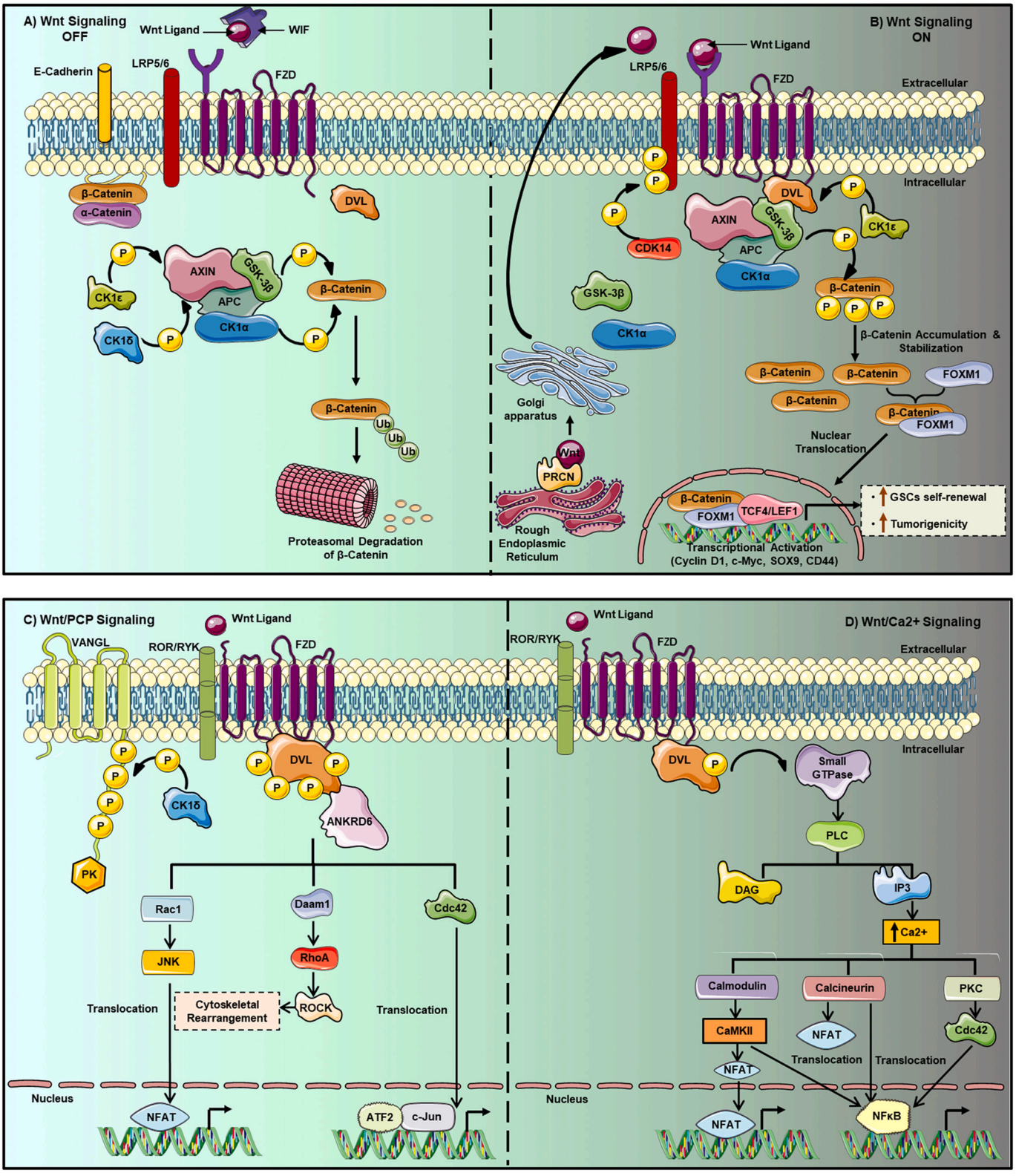

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Fig. 3. (a). A schematic illustration of the canonical Wnt signaling pathway. (A) Left panel displays that Wnt signaling is inactivated in the absence of Wnt ligands. In the absence of Wnt ligands, β-catenin is phosphorylated by the complex composed of scaffolding proteins, including AXIN, APC, DVL and the kinases CK1α and GSK3β. Thereafter, β-catenin is ubiquitinated and targeted for proteosomal degradation. (B) Right panel reveals that Wnt signaling is activated in the presence of Wnt ligands. The binding of Wnt ligands to FZD family of receptors and to LRP5/6 co-receptors stimulates Wnt signaling. The LRP5/6 receptors are phosphorylated by CK1α and GSK3β. Then, DVL proteins polymerize and are stimulated at the plasma membrane suppressing the complex. This results β-catenin aggregation and stabilization in the cytosol, followed by translocation into the nucleus, leading to transcriptional activation of Wnt signaling target genes like c-Myc, cyclin D1, SOX9, CD44 and many more. APC, adenomatous polyposis coli; DVL, dishevelled; CDK14, cyclin-dependent kinase 14; CK1α,ε,δ, casein kinase 1α,ε,δ; GSK3β, glycogen synthase kinase 3β; FZD, Frizzled; LRP5/6, low-density lipoprotein receptor-related protein 5/6; FOXM1, Forkhead box M1; TCF4/LEF1, T-cell factor4/lymphoid enhancer factor1; SOX9, SRY-Box Transcription Factor 9. (b). A schematic representation of the non-canonical Wnt signaling pathway. (C) Left panel shows the Wnt/PCP signaling. Wnt ligands bind to the FZD receptor as well as the ROR/RYK co-receptors. Then, DVL is recruited and triggered, followed by stimulation of VANGL. Thereafter, with the help of the cytoplasmic protein Daam1, DVL binds to the small GTPase RhoA. The small GTPases Rac1 and RhoA consequently activate the activation of ROCK, which will lead to the cytoskeletal rearrangement, and JNK which activates gene transcription via the c-Jun activation. (D) Right panel displays the Wnt/$Ca2^{+}$ signaling. This signaling is instigated when Wnt ligands binds to the FZD receptor and the co-receptor ROR/RYK. Then, DVL is recruited and stimulated and binds to the small GTPase that activated PLC, which increases the $Ca2^{+}$ level via IP3, which in turn stimulates PKC, calmodulin and calcineurin. As a result, PKC, CaMKII and calcineurin phosphorylate NFAT and activate the expression of target genes. PCP and Ca2+ can downregulate the signaling of β-catenin. PCP, planar cell polarity; ROR, bind tyrosine kinase-like orphan receptor; RYK, receptor-like tyrosine kinase; ANKRD6, ankyrin repeat domain 6; VANGL, Van Gogh-like; RhoA, Ras homolog family member A; Daam1, DVL associated activator of morphogenesis; Rac, ras-related C3 botulinum toxin substrate; ROCK, Rho-associated protein kinase; PLC, phospholipase C; IP3, inositol 1,4,5 triphosphate; DAG, diacylglycerol; PKC, protein kinase C; CaMKII, calmodulin-dependent protein kinase II; cdc42, cell division control protein 42; ATF2, activating transcription factor 2; NFAT, nuclear factor of activated T cells; PK, Prickle.

3, which are highly homologous (Massague, 2008). All the three TGF-β isoforms are expressed in malignant gliomas *in vivo* (Karl Frei et al., 2015; Kjellman et al., 2000). However, notorious pathogenic effects in GB have been only attributed to the isoforms TGF-β1 and TGF-β2 while there is not much functional data for TGF-β3 (Eisele et al., 2006; Friese et al., 2004; Seystahl et al., 2017). While TGF-β signaling is widely regarded for its tumor-suppressive functions in epithelial tissues, it also functions as a driver in GB (Katsuno et al., 2013; Massagué, 2008; Rich, 2003; Wick et al., 2001). Glioma pathogenesis has been linked to aberrant TGF-β signaling, with excessive TGF-1 and 2 concentrations reported in GB compared to healthy brain tissue (Platten et al., 2001; Rich, 2003; Wick et al., 2001). Aberrant signaling in GB cells, such as alterations to the PI3K (phosphoinositide 3-kinase), SMAD and FOXG1 (forkhead box G1) signaling pathways mediate resistance to TGF-β-induced cell growth inhibition (Seoane et al., 2004). In GB cells, it is demonstrated that high levels of TGF-β/SMAD signaling induces induction of PDGF-B (platelet derived growth factor-B), thus resulting in tumor cell proliferation (Bruna et al., 2007). Tumorigenic and aggressive behavior of GSCs is reinforced by autocrine TGF-β signaling (Ikushima et al., 2009). Human GSCs have been shown to release more TGF-β2 factor than differentiated glioma cells, and the sheer volume of TGF-β2 secreted happens to be related to the glioma's pathological grade (Qiu et al., 2011). ZEB1 (zinc Finger E-Box binding homeobox 1) is a transcriptional activator of the EMT (epithelial-to-mesenchymal transition) process. It was identified as a potential regulator of GSCs stemness and invasive properties, up-regulating EMT genes, as well as several GSC biomarkers like SOX2 (SRY (sex determining region Y)-box 2) and OLIG2 (Oligodendrocyte lineage transcription factor 2) (Siebzehnrubl et al., 2013). Singh et al., reported that the unphosphorylated variant of the neural transcription factor OLIG2, which is needed for GSC gliomagenesis, triggers infiltration of patient-derived GSCs via TGF-β2 signaling, which strengthens the transcription of EMT-related genes, including TWIST1 (Twist-related protein 1), CREB1 (cAMP responsive element binding protein 1), ZEB1, CD44, and TGF-β2 (Singh et al., 2016). TGF-β is also functional in other GSC-related signaling mechanisms, such as the SOX family of proteins, and has been shown to sustain the population of GSCs. TGF-β plays a role in this by specifically triggering the expression of SOX4, which facilitates SOX2 expression by interacting with the enhancer region of SOX2. SOX2 is an essential factor for maintenance of GSC stemness (Ikushima et al., 2009). Knockdown of SOX2 by siRNA (small interfering RNAs) dramatically reduced the self-renewal capacity and sphere-forming capabilities of GSCs. In orthotopic immune deficient mice, suppression of TGF-β signaling ended up causing downregulation of SOX2 expression, which promotes differentiation of GSCs, deprives GSCs of stemness abilities, and reduces tumorigenicity. Furthermore, Penuelas et al., have shown that TGF-β boosts self-renewal abilities of GSCs via Smad-dependent stimulation of LIF (leukemia inhibitory factor) and the successive initiation of the JAK-STAT (Janus kinase/signal transducers and activators of transcription) signaling (Peñuelas et al., 2009). Song et al., reported that TGF-β signaling induces the expression of miR-182, a microRNA that directly suppresses CYLD (cylindromatosis). CYLD negatively regulates the activity of NF-κB via ubiquitin deconjugation. TGF-β-mediated repression of CYLD results in NF-κB activation, thus further supporting invasion and aggressiveness of glioma (Song et al., 2012). Another study showed that TGF-β signaling also induces miR-10a/10b expression, which stimulates glioma cell migration by PTEN (phosphatase and tensin homolog) suppression (S. Liu et al., 2013). As TGF-β plays a major role in GB progression, targeting TGF-β or its downstream signaling factors might be a promising therapeutic approach.

4.3. TLR signaling pathway

Toll-like receptors (TLRs) play a critical role in the innate immune system. Endogenous substances released from wounded tissues or via PAMPs (pathogen-associated molecular patterns), for example, LPS, initiate TLR signaling in the course of infection or injury of the tissues (Hanke and Kielian, 2011). The Toll gene was first identified in *Drosophila melanogaster* and was shown to regulate dorsoventral polarity during the initial phases of embryogenesis and innate immunity (Anderson et al., 1985). To date, about 13 TLR genes have been recognized in mouse and human genomes. TLR1 to 10 are functional in humans, whereas TLR1 to 9 and TLR11 to 13 are functional in mice (Hopkins and Sriskandan, 2005). TLRs are necessary for microglia to initiate the immune responses in the CNS (Olson and Miller, 2004). TLR2, 4, and 9 were investigated for their expression on glioma cells, and their function in tumor growth has mostly been identified as tumor-promoting (Herrmann et al., 2014; Sarrazy et al., 2011; Tewari et al., 2012; Vinnakota et al., 2013; C. Wang et al., 2010). TLR2, 3, 4, and 9 were also shown to be extensively expressed both on healthy and tumor-infiltrating microglia in the brain parenchyma. Despite similar levels of TLR expression, the tumor microenvironment has a significant impact on the mechanism of infiltrating microglial cells (Hussain et al., 2006; Meng et al., 2008). Throughout gliomagenesis, TLR signaling plays a significant role in controlling microglial activities (Fig. 5). The MT1-MMP, for example, is a microglial enzyme that regulates the activities of several growth factors in neo-vascularization, and its involvement revealed that microglia positively correlates with glioma growth. Markovic et al., reported that treatment of primary microglia with TLR2 agonist increased the expression of downstream signal molecules such as MyD88 (Myeloid differentiation primary response 88) and p38 MAPK (p38 mitogen activated protein kinases), which stimulated the release of MT1-MMP and MMP-9, contributing to glioma infiltration by ECM degradation (Markovic et al., 2009). In addition, blocking the TLR2

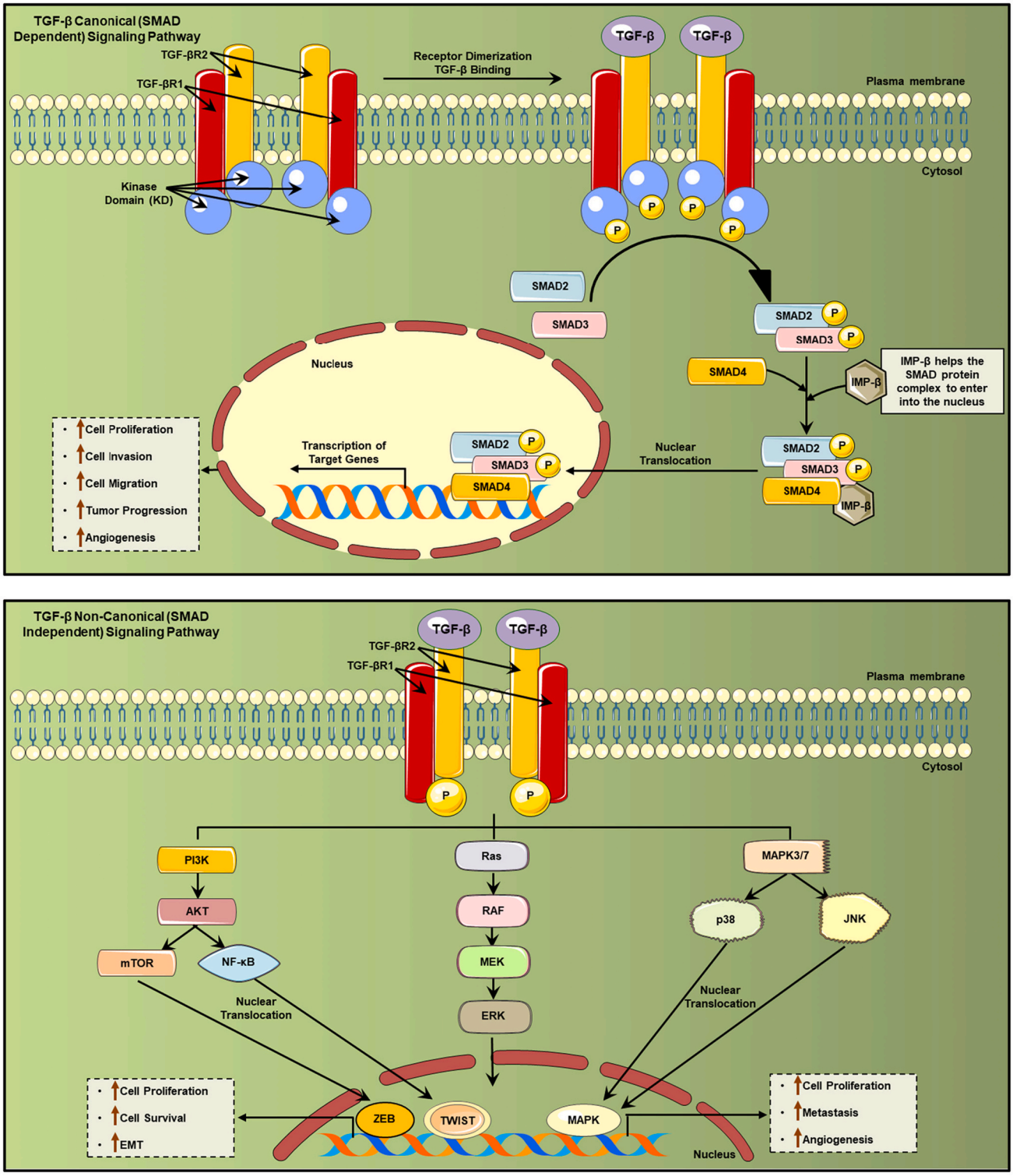

Fig. 4. (a). A schematic representation of the TGF-β canonical (SMAD dependent) signaling pathway. In the TGF-β/SMAD signaling pathway, biologically active TGF-β ligands bind to type I/II TGF-β receptors induces phosphorylation, and thereby activation of receptor-mediated SMAD2/3 proteins. These proteins are phosphorylated at C-terminal serine residues and form complexes with SMAD4 (co-SMAD). These protein complexes then translocate to the nucleus, where they bind to site-specific recognition sequences within the promoter regions of target genes, thereby regulating their transcriptional activities. TGF-BR, transforming growth factor β receptor; SMAD, intracellular protein; IMP-β, importin-β. (b). A schematic representation of the TGF-β non-canonical (SMAD independent) signaling pathway. In the TGF-β non-canonical signaling pathway, the TGF-β signaling activates various SMAD independent pathways like PI3K/AKT, ERK/JNK/p38 MAPK and NF-κB. PI3K, phosphoinositide 3-kinases; AKT, protein kinase B; mTOR, mammalian target of rapamycin; RAF, rapidly accelerated fibrosarcoma; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; MAPK, mitogen-activated protein kinase; JNK, Jun N-terminal Kinase; ZEB, zinc Finger E-Box binding homeobox; TWIST, twist-related protein.

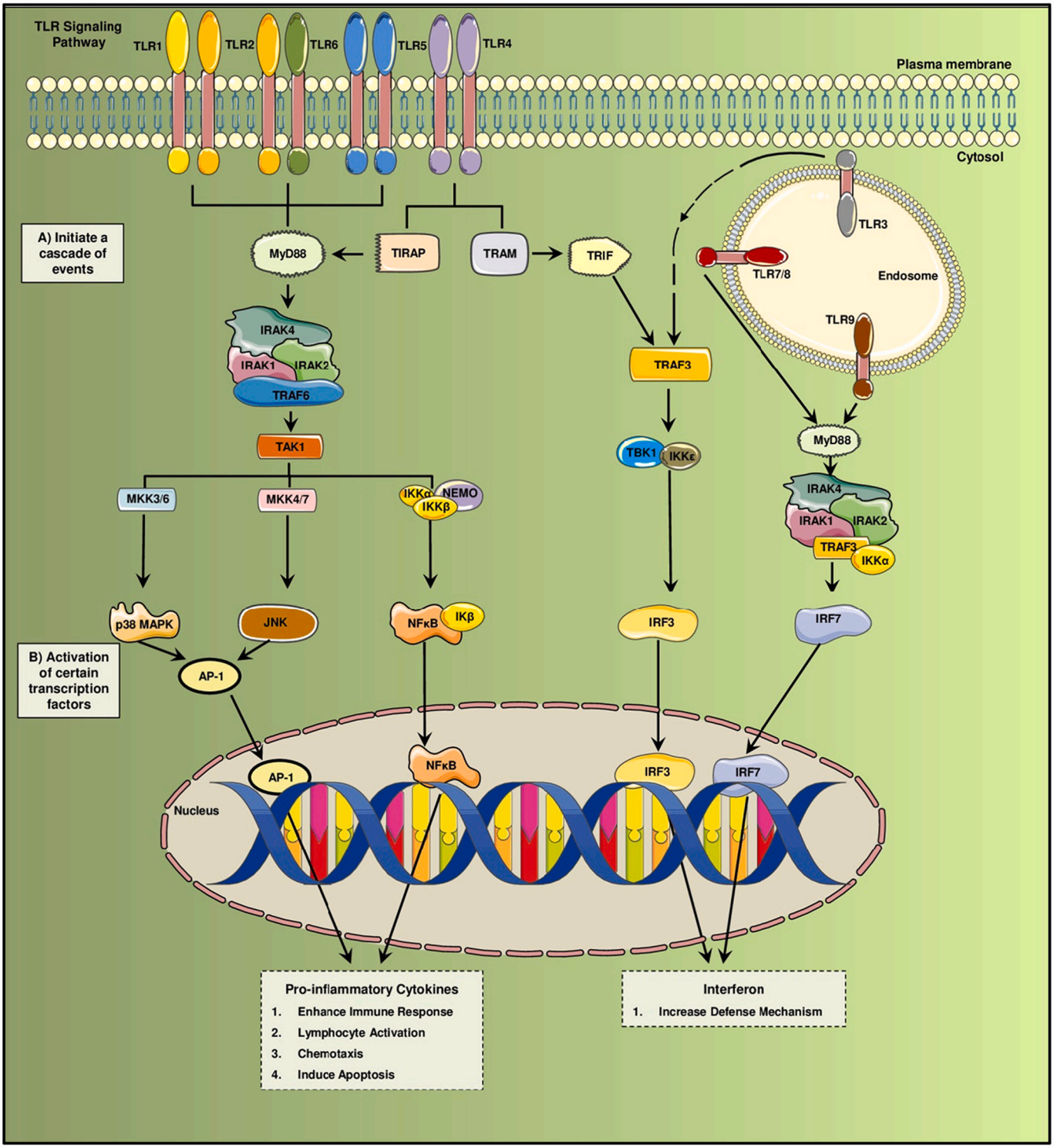

Fig. 5. A schematic illustration of the cell surface and endosomal TLR signaling pathway. TLR1, 2, 4, 5, and 6 are expressed on the cell surface and mainly identify cell wall components and/or microbial membrane, while TLR3, 7, 8, and 9 are expressed in the membranes of endolysosomal compartments and recognize nucleic acids. TLR-1 and 6 recognize their ligands as heterodimers with TLR-2. Conversely, TLR3, 4, 5, 7, and 9 deliver their signals by forming homodimers after interacting with their specific ligands. TLRs have a variable number of ligand-sensing, cytoplasmic TIR domains and a leucine-rich repeats (LRRs) at their N-terminal ends. The TIR domain is involved in the regulation of TLR signaling by mediating interactions between TLRs and adaptor proteins, such as MyD88, TIRAP, TRAM and TRIF (MyD88 independent pathway), to facilitate the expression of pro-inflammatory chemokines, cytokines, and interferon's. MyD88, myeloid differentiation factor 88; TIRAP, toll/interleukin-1 receptor domain-containing adapter protein; TRIF, TIR-domain-containing adapter-inducing interferon-β; TRAM, TRIF-related adaptor molecule; IRAK, interleukin-1 receptor-associated kinase 4; TRAF, TNF receptor-associated factor; TAK1, transforming growth factor β–activated kinase 1; MKK, MAPK kinase; IKKα, β, ε, IκB kinase; TBK1, TANK-binding kinase 1; NEMO, NF-κB essential modulator; AP1, activator protein 1; IRF, interferon regulatory factors.

signaling on microglia or elimination of microglia MT1-MMP decreased the expression of MT1-MMP on microglia and hampered glioma progression (Markovic et al., 2009). This proposes that the stimulation of the TLR 2 signaling on microglial cells augments infiltration of tumorigenic cells inside the brain. Glioma-generated versican, a large extracellular matrix proteoglycan, as an endogenous TLR2 ligand is capable of initiating p38 MAPK stimulation in microglial cells, resulting in increased MT1-MMP production. TLR2 expression has also been observed in human GB U87 cell lines using touchdown PCR (TD-PCR) and has been associated with tumour progression (Haghparast et al., 2011). TLR4 signaling was also found to be implicated in the regulation of various biological mechanisms such as proliferation, migration, survival and immune evasion, as well as resistance to TNF-α treatment. TLR4 was either directly associated with these processes or altered their final result. Expression of TLR4 has been found in various glioma cell lines, such as U87, U118, LN229, and A172 (Gupta et al., 2013; Sarrazy et al., 2011; Tewari et al., 2012). Through western blot and immunohistochemistry analysis, Tiwari et al., found that the expression of proteins in primary biopsies from GB individuals was elevated relative to adjacent non-neoplastic tissue (Tewari et al., 2012). A recent study has shown that the absence of TLR4 expression suppresses the development of U-87 tumor xenografts. In addition, deficiency of the TLR4 gene induced apoptotic cell death, leading to a reduction in tumor growth. TLR4 appears to be a pivotal marker for tumor prognosis and metastasis (Casili et al., 2018). A surprisingly new finding by Alvarado et al., demonstrated that the downstream signaling pathway of TLR4 stayed dynamically active in spite of TLR4 inactivation. The critical proteins, such as TBK1 (TANK binding kinase 1) and the transcription factor RBBP5 (retinoblastoma binding protein 5) are highly expressed in GB cells, and specifically, in self-renewing CSCs. Inhibition of RBBP5 could activate the TLR4 signaling cascade, which may be a very viable one, as well as a new target for therapeutics. This may enable the suppression of stem cell-like characteristics in CSCs, potentially inhibiting glioma formation. Alvarado and colleagues employed this new hypothesis in an orthotropic murine model. Inhibiting the expression of RBBP5 in CSCs with shRNA (short hairpin RNA) culminated in an increase in mouse survival rate as compared to controls (Alvarado et al., 2017).

4.4. STAT3 signaling pathway

STAT3 (signal transducer and activator of transcription 3) is an intracellular cell signaling protein that is one of 7 members of the STAT family of proteins, which comprises STAT1, 2, 3, 4, 5a, 5b, and 6 (Ouédraogo et al., 2017). STAT2, 4 and 6 are active in immune system regulation and functions, while STAT1, 3 and 5 were linked with immunological activities as well as alteration and development of neoplastic cells in several tumors, including GBs (Mostofa et al., 2017; Ouédraogo et al., 2017). STAT3 controls the expression of a variety of genes implicated in cell cycle, cell survival, and cancer malignancy. STAT3 translocate to the nucleus after activation, where it aids in the translation of target genes involved in angiogenesis, anti-apoptosis, invasion, and migration (Fig. 6) (Furtek et al., 2016). A significant proportion of GB tissues and cell lines exhibit constitutive STAT3 phosphorylation compared to the healthy brain (Brantley et al., 2008; G. S. Lin et al., 2014; Luwor et al., 2013; Schaefer et al., 2002). This continuous STAT3 activation might occur by specific functional abnormalities or increased expression of upstream cytokine and growth factor receptor signaling, or maybe deficits in the negative feedback system. Stimulation of STAT3 on a continuous level facilitates the aggregation of tumor-associated microglia, which suppresses anti-tumor pathways and causes resistance to tumor antigens, as well as possessing a pro-angiogenic capacity (Fernando O. Martinez and Gordon, 2014; Su et al., 2018). Tumor-associated microglia releases a variety of factors, including PDGF, EGF, TGF-β and FGF-2 (Fibroblast growth factor-2) that

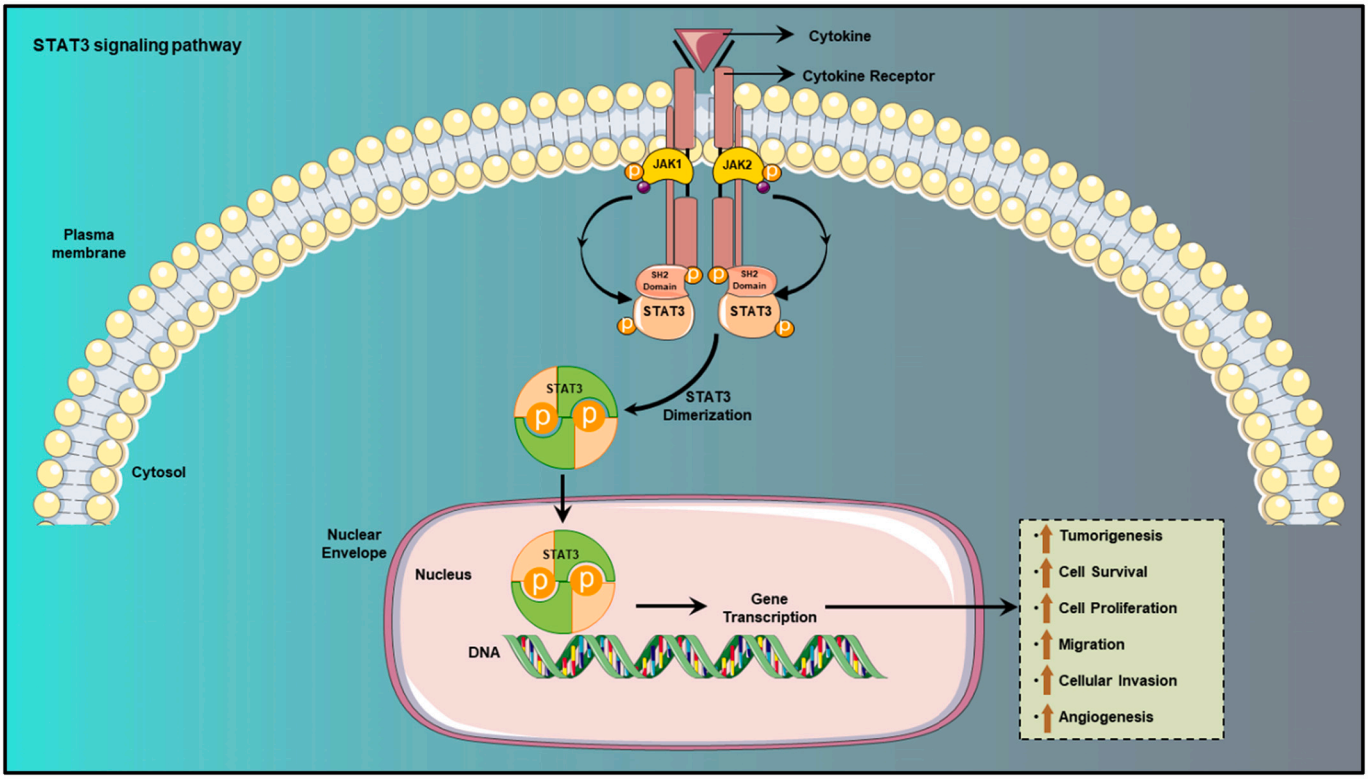

Fig. 6. A schematic illustration of the STAT3 signaling pathway. Upon binding to the membrane receptors, the cytokines trigger downstream signaling cascades via the JAK-STAT signaling. Cytokine receptor homodimers or heterodimers phosphorylate and stimulate JAKs, which act as a platform for the stimulation of unphosphorylated STAT3. Phosphorylated STAT3 dimers are translocated into the nucleus where they promote transcription of a number of genes that may contribute to tumorigenesis, cell survival, proliferation, migration and invasion.

stimulates the STAT-3 pathway in tumorigenic cells and GSCs, increasing their progression (Fernando O. Martinez and Gordon, 2014). According to several studies, activation of S100B-RAGE-STAT3 signaling promotes M2 polarization. S100B (S100 calcium binding protein B) secreted by tumors stimulates RAGE (receptor for advanced glycation end products) on microglial cells, resulting in STAT3 initiation and inhibition of microglial M1 activity, which consecutively inhibits the production of IL-1β and TNF-α (L. Zhang et al., 2011). According to Zhang et al., suppression of RAGE expression in microglial cells blocked glioma-induced STAT3 expression and the development of M2-type cytotoxic factors, including IL-10 (L. Zhang et al., 2011). In addition, the stimulated RAGE signal in microglia and/or macrophages affects angiogenesis as well as retaining the M2-like phenotype characteristics. Another study by Chen et al., discovered that genetically depleting RAGE in mice and glioma cells inhibits the process of angiogenesis via downregulating the expression of VEGF (X. Chen et al., 2014). In summary, progression and development of GB tumor cells is strongly dependent upon the activation of STAT3 for proliferation, mesenchymal transition and invasion with prognostic values. Phosphorylation of STAT3 is also potentially linked with immune evasion and GSC phenotypes, as it regulates the tumor milieu, which contributes to tumor resistance and recurrence to standard treatments. The absence of *in vivo* and *in vitro* tumor heterogeneity models makes selective targeting of STAT3 signaling for glioma management one of the greatest obstacles (da Hora et al., 2019).

4.5. PYK2 signaling pathway

Pyk2 (proline-rich tyrosine kinase 2) is a non-receptor tyrosine kinase in the FAK (focal adhesion kinase) family (Du et al., 2001). Pyk2 is also termed as RAFTK (related adhesion focal tyrosine kinase), CAK β (cell adhesion kinase β), and calcium-dependent tyrosine kinase (CADTK). It can be activated by neuropeptides, hormones, cytokines and chemokines (Avraham et al., 1995; Lev et al., 1995; Sasaki et al., 1995; Yu et al., 1996). Pyk2 links with different signal transduction cascades and portrays crucial roles in cell motility and invasion (Fig. 7) (Dunty and Schaller, 2002; Lipinski et al., 2005; Paulino et al., 2010; Riggs et al., 2011; Verma et al., 2015). Pyk2 has a three-domain structure that is linked with progression of tumor cells, namely NH2-terminal FERM (F for 4.1 protein, E for ezrin, R for radixin and M for moesin) domain, C-terminal focal adhesion targeting (FAT) domain and centrally located kinase domain (Lipinski and Loftus, 2010). The FERM domain at the NH2-terminus is essential for Pyk2 kinase expression and receptor association functions (Dunty and Schaller, 2002). The FAT domain at the C-terminus of Pyk2, which has auto-phosphorylation site Tyr881, is linked with the MAPK signaling pathway and tumor progression (Blaukat et al., 1999; Kuang et al., 2013). And the centrally located kinase domain of Pyk2 could be useful in the development of specific kinase blockers for the treatment of cancer (Han et al., 2009). Increased expression of Pyk2 initiates in many types of tumors and it facilitates tumor progression. Pyk2 overexpression occurs in 84.1% of GB (Gutenberg et al., 2004). Upregulated Pyk2 significantly increases glioma cell migration (Lipinski et al., 2003). Soluble factors, expressed by microglial cells enhance the migration of gliomas by increasing the phosphorylation levels of Pyk2 at Tyr 579/580 (Rolón-Reyes et al., 2015). Glioma cell migration requires auto-phosphorylation of Pyk2 Y402 and the N-terminal FERM domain of Pyk2 (Lipinski et al., 2005). Orai 1 (ORAI calcium release-activated calcium modulator 1), the key component mediating store-operated $Ca2^{+}$ entry, controls glioma cell focal adhesion turnover and EMT via the Pyk2 pathway (M. Zhu et al.,

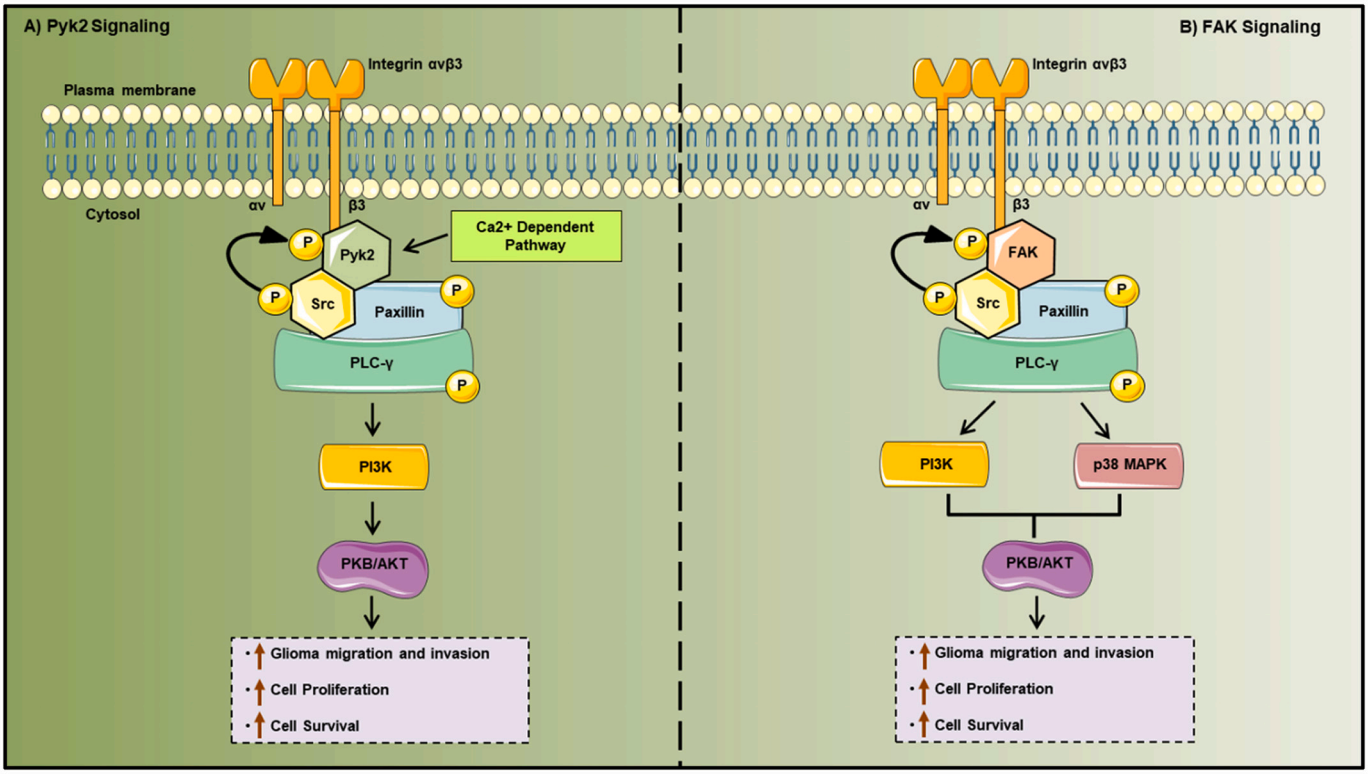

Fig. 7. A schematic illustration of the putative integrin signaling pathway via pyk2 and FAK. Integrins are transmembrane heterodimer receptors consisting of α and β subunits. (A) Left panel displays Pyk2 signaling and (B) the right panel displays FAK signaling. In response to integrin αvβ3 activation, Pyk2 and/or FAK are recruited to a signaling complex composed of Src, paxillin and PLC-γ. Pyk2 can be phosphorylated via Src or other $Ca2^{+}$ dependent pathways, but FAK is only phosphorylated via Src. Then, Pyk2 and/or FAK may result in stimulation of PI3K and/or p38 MAPK, which may lead to increased cell proliferation, survival, migration and invasion. Pyk2, proline-rich tyrosine kinase 2; FAK, focal adhesion kinase; Src, SRC proto-oncogene, non-receptor tyrosine kinase; PLC-γ, phosphoinositide phospholipase C; PI3K, phosphoinositide 3-kinase.

2014). Lipinski et al., have shown that knockdown of Pyk2 inhibits glioma distant metastasis and improves the survival rate of orthotopic glioma xenografts (Lipinski et al., 2008). Another study showed that the downregulation of focal adhesion kinase family interacting protein (FIP200) enhances the auto-phosphorylation levels of Pyk2 at Tyr402, which plays a role in inducing apoptosis of GB cells (D. Wang et al., 2011). In addition, a study by Loftus et al., reported that miR-23b also significantly suppresses the migratory and invasive properties of gliomas by targeting the 3'UTR of Pyk2 (Loftus et al., 2012). Lately, by using western blot technique, Kimberleve et al. observed upregulation of Pyk2 at Tyr579/580 in rodent glioma model (C6 and GL261) and in three different glioma cell lines (U-87 MG, A172 and HS683). SiRNA knockdown of Pyk2 protein and pharmacological inhibition by Pyk2/FAK inhibitor PF-562, 271 upturned the stimulating effects of microglial cells on glioma migration in all cell lines (Rolón-Reyes et al., 2015). FAK, a Pyk2 relative that is active in tissue migration, was shown to be expressed in glioma cells. FAK's function in the migration of gliomas has been reported to be contradictory. According to two studies, FAK does not promote migration (Lipinski et al., 2005; Rolón-Reyes et al., 2015) while other two studies indicated that it does promote glioma cell migration (Lindemann et al., 2011; Yang et al., 2011). In sum, all these findings propose that microglial cells stimulate the migration of gliomas through the Pyk2 signaling pathway. Nonetheless, relatively few reports have been published to date regarding the association of microglial cells in Pyk2 signaling in GBs.

5. Therapeutic strategies for glioblastoma

5.1. Immunotherapy

Several immunological therapies have recently been identified as having the ability to facilitate brain tumor therapy. A study by Poli et al., demonstrated that primed NK (natural killer) cells together with the antibody mAb 9.2.27 reduced tumor progression by restricting growth and spurring apoptotic cell death (Poli et al., 2013). Moreover, in nude mice, a recombinant immunotoxin product has been shown to inhibit the folate receptor β on macrophages and microglia as well as suppress glioma growth (Nagai et al., 2009). Another immunotherapeutic way to improve anti-tumor therapy in the brain is to upregulate M1 microglia and/or macrophage activities. Certainly, IFN-γ, IL-12 and LPS effectively, increased microglial cells' phagocytic and cytotoxic activities that eliminated tumor progression *in vivo* (Chiu et al., 2011; Mora et al., 2009). Likewise, activation of M1 microglia and/or macrophages by the TLR3 agonist poly (I:C) stimulated apoptosis and blocked tumor growth and invasion (Kees et al., 2012). In addition, blockade of CSF-1R (colony stimulating factor 1 receptor) signaling in GB mice via anti-CSF-1R antibody pexidartinib (PLX3397) caused a dramatic decline in M2 macrophage polarization and inhibits tumor growth as well as a considerable surge in the survival duration of the treated mice (Pyonteck et al., 2013). Later, another study found no efficacy of PLX3397 against recurrent GB (Butowski et al., 2016). In GB mice, another CSF-1R inhibitor, BLZ945, decreased M2-like markers expression in GAMs, and supplementation with IGF-1 (insulin-like growth factor 1) and PI3K antagonist increased survival and decreased tumour progression rate (Coniglio et al., 2012). Another research found that inhibiting both CSF-1R and IGF-1R/PI3K greatly improves survival outcomes in mice with recurrent GB (Quail et al., 2016).

5.2. Nanoparticles-based therapy

The development of nanoparticles has greatly aided in the detection and management of brain tumors (Glaser et al., 2017). Nanoparticles have gained considerable attention because of their high drug loading potential and protection against enzymatic and chemical degradation. They have extensive therapeutic benefits and have emerged as a revolutionary tool in nanomedicine relative to conventional drug delivery techniques (Couvreur et al., 2002). The potential of nanoparticles to be complex with receptor ligands or biomolecules may increase their specificity towards the tumorigenic environment and the deployment of tumor-targeted radioisotopes. Since the microenvironment between normal and malignant tumor cells differs, the development of nanoparticles with molecules and proteins targeting abundantly expressed tumorigenic factors, receptors and biological pathways is a potential domain of nanoparticle-based research (Hernández-Pedro et al., 2013). Both GB and GAMs have become promising targets of radionuclide transporters, however, with no positive results till now.

Recently, magnetic nanoparticles (MNPs) have received noteworthy recognition due to their remarkable ability as an important element in MRI (magnetic resonance imaging) technique and as a heating mediator in hyperthermia therapy (Ito et al., 2005). MNPs such as iron oxide NPs (IONPs), fluorescent MNPs and superparamagnetic iron oxide NPs (SPIONs) are widely used as diagnostic imaging agents and therapeutic delivery vehicles (Sun et al., 2008). MNPs comprise an inorganic iron oxide core and a biocompatible surface layer that is suitable for physiological conditions (McNeil, 2005). MNPs can perform numerous functions concurrently, including drug delivery, multimodal imaging, real-time monitoring and combined therapeutic methodologies (Frullano and Meade, 2007). Some of the well-known techniques that have been used for the MNP synthesis are chemical vapor deposition, microemulsion, solvothermal, sonochemical, co-precipitation, microwave-assisted, thermal decomposition, combustion, and carbon curve and laser pyrolysis synthesis (Akbarzadeh et al., 2012). Ling et al., synthesized a multifunctional nanotheragnostic system by coating temozolomide (TMZ)-loaded PLGA-based SPIONs with polysorbate 80. This new system exhibited excellent controlled release of TMZ for about 15 days (Ling et al., 2012). The EGFR represents a primary therapeutic target as it is commonly overexpressed in malignant glioma. SPIONs conjugated to recombinant human EGF (SPION–EGF) were invented by Stevtsov and colleagues (Shevtsov et al., 2014). The SPION–EGF conjugates were later used as an agent for MRI contrast enhancement of EGFR-overexpressing C6 gliomas. The conjugate showed no harmful effects and high intracellular integration was observed on C6 cell proliferation and viability. Administration of the prepared SPION–EGF conjugates via intravenous route provided targeted delivery across the BBB in animals. In another study, Kaluzova et al., synthesized multifunctional IONPs conjugated with cetuximab (CET), an EGFR inhibitor (Kaluzova et al., 2015). They later demonstrated their targeting activity with EGFR and EGFRvIII (epidermal growth factor receptor variant III)-expressing neurospheres and GSCs. The prepared CET-IONPs were shown to have a significant anti-tumor effect compared with CET alone due to EGFR internalization, EGFR signaling alterations and induction of apoptosis in EGFR-expressing GSCs and human glioblastoma neurospheres. Richard et al., have developed a new nanosystem to target overexpressed αvβ3 integrin in brain tumors (Richard et al., 2017). They functionalized IONPs with phosphonate poly (ethylene glycol) POPEG-COOH to increase the stability of NPs in the biological media. Under microwave conditions, the carboxylate end characteristics were further grafted with cRGD (cyclic arginine-glycine aspartic) peptide. It was identified that the vigorous targeting triggered via cRGD onto the surface of NPs caused the accretion of the organized nanoplatforms in tumor tissue one day after injection. SPIONs based multimodal theragnostic nanoplatforms containing antitumor drug doxorubicin and fluorescent dye Rhodamine B isothiocyanate for theragnostic analysis were developed by Wang et al., (X. Wang et al., 2016). This nanoplatform was further conjugated with tumor-specific ligand transferrin (Tf) and was delivered into U251 MG GB cell lines to access its biological effects. The results indicated that the nanoplatform could efficiently suppress the proliferation and initiate apoptosis in the treated U251 MG GB cells. Furthermore, Hua et al., developed three different types of MNPs (MNP1, 2, and 3) by varying the concentration of polymer poly-[aniline-co-N-(1-one-butyric acid) aniline] (SPAnH) used for coating of iron oxide (Fe3O4) cores (Hua et al., 2011). These MNPs have been designed to improve the clinical

effectiveness and thermal efficiency of BCNU (1,3-bis (2-chloroethyl)-1-nitrosourea). Their results also revealed that using an external magnetic field increases the concentration of bound-BCNU-3 at the target site *in vitro* and *in vivo* (Hua et al., 2011). It could therefore be a promising strategy for transporting drugs across the blood brain barrier (BBB) by using an external magnet. Furthermore, Cordier et al., stated that tagging nanoparticles with a substance P (SP) antagonist is a potential strategy; however, more studies and investigations are required (Cordier et al., 2014). Moreover, it was also hypothesized that the enrollment of GAMs by tumorigenic cells may be a possible option for the delivery of drug molecules (Phillips et al., 2014). In sum, all the above studies indicate that nanoparticles present great potential as a theranostic system for brain tumor targeting and are considered to be a promising therapeutic technology for brain tumors.

5.3. Antibiotic therapy

Antibiotic drugs can be used as an efficient therapeutic alternative for glioma treatment by modulating the functions of microglia and macrophages. Minocycline hydrochloride, a lipophilic antibiotic, interferes with the activation of microglia by suppressing the p38 MAP kinase and MT1-MMP expression in microglial cells (Markovic et al., 2011; Weingart et al., 1995). When systemic BCNU was supplemented with minocycline to inhibit the activation of microglia in a rat model of glioma, synergistic effects were observed (Frazier et al., 2003). Furthermore, cyclosporine treatment dramatically reduced the levels of GM-CSF and IL-10, which inhibited microglia/macrophage invasion and reduced the growth of glioma (Gabrusiewicz et al., 2011). Amphotericin B was shown to stimulate microglia/macrophages activation, contributing to the interruption of the brain tumor-initiating cell-cycle and cell differentiation inhibition (Sarkar et al., 2014).

5.4. Radiation therapy

In general, radiation is the first-line treatment for a multitude of brain tumors. Though the implementation of radiation therapy faces serious roadblocks in cancer management due to the need to administer an adequate amount at the tumor site without destroying the normal adjacent tissues (Zhao et al., 2016). According to Vatner and colleagues, the anti-tumor effects of radiotherapy in the tumor environment are still uncertain (Vatner and Formenti, 2015). In addition, the mobilization of TAMs in the glioma region is heightened after radiotherapy (Vatner and Formenti, 2015). Wang et al., recently published a report that explored a connection between radiotherapy resistance and M2 glioma infiltrating macrophages (Q. Wang et al., 2017). Tumor secreted stroma cell-derived factor 1 (SDF-1) is one of the most significant factors in radiotherapy induced invasiveness, where it employs its chief activities via revascularization of tumors and mobilization of macrophages (S. C. Wang et al., 2013). However, by using a combination of radiotherapy and an inhibitor of SDF1 (AMD3100) abrogated regrowth of tumorigenic cells in nude mice by preventing radiotherapy-induced macrophage recruitment (Kioi et al., 2010).

5.5. CAR-T based therapy

Chimeric antigen receptor T cell (CAR-T) therapy is a genetically modified molecule expressed on leukocytes (Zhai et al., 2019). CARs are synthetically engineered immunological receptors that guide T cells to destroy malignant tumors by targeting surface proteins expressed on tumorigenic cells. CARs are chimeric proteins and typically consist of 3 major constituents: the extracellular domain accountable for antigen recognition, an intracellular domain accountable for signaling, and a region linking these two components for stability, flexibility and dimerization potential comprised of the transmembrane domain and extracellular spacer (Priceman et al., 2015; C. Zhang et al., 2017). Since CAR-T therapy has established new ways of targeted management, various CARs targeting glioblastoma have been designed, including IL13Rα2 (IL13 receptor α2), HER2 (human epidermal growth factor receptor 2), and EGFRvIII (Bagley et al., 2018).

The very first CAR-T cells were produced and evaluated for malignant tumors directed at IL13Rα2. Expression of IL13Rα2 was shown to accelerate with malignancy, to be a predictive marker of low survival rates, and to be linked with gene signatures describing the mesenchymal subclass of GB (Brown et al., 2013; Jarboe et al., 2007). IL13Rα2 is not expressed at relatively high levels in normal brain tissues (Debinski et al., 1999; Jarboe et al., 2007), but it is expressed both by GSCs and differentiated tumor populations, which make malignant subpopulations prone to CAR-T cell cytotoxicity (Brown et al., 2012). First generation IL13-zetakine $CD8^+$ T cell clones were tested in two FDA-authorized clinical trials utilizing allogeneic (NCT01082926, six patients) and autologous (NCT00730613, three patients) engineered T cells for non-resectable and resectable recurrent GB, respectively (Brown et al., 2015; Keu et al., 2017; Yaghoubi et al., 2009). Recently, a phase 1 clinical trial (NCT02208362) investigating 2^{nd} generation IL13Rα2-targeted, 4-1BB (CD137, TNFRSF9) co-stimulatory CAR-T cells in individuals with relapsed/refractory (r/r) IL13Rα2^+ malignant glioma demonstrated regression of all intracranial and spinal lesions in patients with recurrent multifocal GB (Brown et al., 2016). Anti-tumor potency and viability of these CAR-T cells have been elevated relative to 1^{st} generation IL13Rα2 CAR-T cells in glioblastoma mouse models (Brown et al., 2016).

HER2 is abundantly expressed in certain cases of GB. With the use of the orthotopic murine GB xenograft model, Ahmed et al., have shown that the infusion of HER2 CAR-T cells contributes to proliferation of T cells and IFN-γ and IL-2 secretions, facilitating the regression of HER2-positive GB (Ahmed et al., 2010). Furthermore, a recent phase 1 dose-escalation analysis (NCT01109095) confirmed the safety of autologous HER2-CAR virus-specific-T cells in 17 individuals with progressive GB. Of eight individuals, seven had a stable disease and one had a partial response. The median survival rate was 11.1 months. This HER2-CAR-T cell clinical therapy offers initial signs of safety, but also highlights the necessity for enhanced proliferation, function, and durability of HER2-CAR-T cells (Ahmed et al., 2017). In addition, antigen escape variants may result in tumor recurrence following CAR-T treatment. However, tandem CAR-T cells, including those targeting IL13Rα2 and HER2, can maximize anti-tumor effectiveness, minimize antigen escape, and improve survival in GB models (Hegde et al., 2016).

Additionally, it was found that there is an overexpression of EGFR in GB. And EGFRvIII is a mutation that frequently occurs in GB. EGFRvIII, a genetic mutation most frequently observed in gliomas, has a truncated extracellular domain that contributes to constitutive signal stimulation and is consistent with GB growth (Fan et al., 2013). This truncated variant offers a novel, tumor-specific immunogenic epitope for generating scFv (single-chain variable fragment)-based CAR targeting domains and, owing to its tumor-restricted expression. EGFRvIII is probably one of the most extensively studied CAR targets for GB (B. D. Choi et al., 2014; Morgan et al., 2012; O'Rourke et al., 2017; Sampson et al., 2014). A dose escalation analysis of EGFRvIII CAR-T cells in recurrent EGFRvIII$^+$ GB employing a 3^{rd} generation human scFv-based EGFRvIII CAR with CD28 and 4-1BB co-stimulation (NCT01454596) (Goff et al., 2019; Morgan et al., 2012). At initial dose levels (107−109 cells), EGFRvIII-CAR-T cells were very well-tolerated, with no signs of off-tumor targeting of EGFR. At the highest dose levels of $\geq 10^{10}$ T cells, pulmonary toxicities have been reported, as well as one treatment associated mortality following IV infusion of 6×10^{10} cells, resulting in respiratory symptoms within hours of cell infusion (Goff et al., 2019). Scientists at the University of Pennsylvania have constructed a humanized EGFRvIII-specific CAR and have demonstrated that it has been effectively targeted orthotopically implanted EGFRvIII$^+$ GB in preclinical models. The scFv was designed for the specificity towards EGFRvIII over the wild-type EGFR, and exhibited limited selectivity to human skin grafts *in vivo* and primary human tissue *in vitro* (L. A. Johnson et al.,

2015). This CAR framework has been employed in the EGFRvIII-CAR-T phase 1 clinical trial (NCT02209376) in which 10 individuals with EGFRvIII^{+} GB administrated a single dose of 1.75-5 $\times$ 10^{8} cells injected intravenously former to resection with the aim of understanding activity and safety of CARs (O'Rourke et al., 2017). Examination of the resected tumor post CAR-T cell infusion has shown that IV-infused CAR-T cells have been trafficked to the brain and has also shown a down-regulation of EGFRvIII expression in the recurrent tumors indicating antigen-specific activity. This study also reveals significant obstacles to CAR-T treatment, including tumor heterogeneity and the suppressive tumor microenvironment. Baseline expression of EGFRvIII in GB individuals was heterogeneous, so CARs directed only a segment of the cancer cells and relapse tumors developed that had reduced EGFRvIII levels. Furthermore, the EGFRvIII CAR-contained ICOS (inducible co-stimulator) signaling domain also displayed effective anti-tumor function against EGFRvIII expressing gliomas (Shen et al., 2013). A clinical trial using nimotuzumab revealed similar anti-tumor activity facilitated by EGFR inhibition (Hong et al., 2012).

6. Closing remarks

In and around brain tumors, a highly significant amount of microglia and macrophages are evident. These cells attain alternatively stimulated phenotypic characteristics with potent tumor-tropic properties that aid growth and invasion of GB cells. In general, microglial cells act as a navigator, directing the lymphocytes to the target area and performing their effector roles and scavenge glioma cells. Innate immune responses mediated via microglial cells during the initial stages of gliomagenesis may be helpful, resulting in the activation of successful adaptive immune surveillance and the removal of these cells. However, during an advanced stage of malignancy, where tumorigenic cells have managed to evade the immunoediting process, the microglial cells are altered by certain tumorigenic cells, which later exhibit a completely unique molecular profile, primarily regulating tumor supportive characteristics and eventually promoting tumor progression. Throughout recent years, several attempts have been made to understand the heterogeneity of microglial cells. Research has shown that microglial cells perform an indispensable role in promoting GB growth and progression. While much research has been done on the origin, morphology and functional properties of microglial cells, there have been very limited insights into the dynamic interactions and relationship between GB and microglial cells, as well as how this interaction positively regulates tumor development and adversely impacts patient health outcomes. More recently, the approach to studying gliomagenesis has been directed to a broader scope, considering the microenvironment in which the tumorigenic cells develop and evolve, especially the GSC niche, rather than the glioma cell with its alterations. Such considerations may contribute to novel treatment strategies for GB that might inhibit glioma growth through the modulation of its environment, for example by enhancing the immune responses against the tumor cells. As a result, any immunotherapy that can transform the M2-like phenotype state of GAMs to an M1-like phenotype would likely work the best.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2021.577633.

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