Oligodendrocyte Progenitor Cells in the Tumor Microenvironment

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Abstract

Glioblastoma (GBM) develops from adult brain white matter and is the most common and lethal primary brain tumor, characterized by rapid growth and invasion. GBM tumors frequently spread into the contralateral hemisphere, including in the beginning of tumor development. However, after complete resection of the tumor mass and chemo-radiotherapy, GBM commonly recurs around the tumor removal site, suggesting that the microenvironment at the tumor border provides therapeutic resistance to GBM cells. To improve patient prognosis, understanding the microenvironment at the tumor border is critical. Several microRNAs (miRNAs) show higher expression at the tumor border, with the top three involved in oligodendrocyte differentiation. Oligodendrocyte progenitor cells (OPCs) may induce stemness and chemo-radioresistance in GBM cells, providing a supportive function to promote GBM. This review describes important features of OPCs and insights into the "border niche," a unique microenvironment that allows GBM cells to survive and recur at the tumor border.

Keywords

Border niche · Glioma-associated oligodendrocyte · Oligodendrocyte progenitor cell · Oligodendrocyte · Microenvironment · Glioblastoma · Recurrence · Neuron · Microglia · Macrophage · microRNA · Stemness · Chemo-radioresistance · Invasion · Niche

8.1 Introduction

The major cell types in the brain are neurons, glia such as astrocytes, oligodendrocytes derived from the neuroepithelium, and microglia derived from erythromyeloid cells in the yolk sac during the early developmental stage [32, 76]. Glioblastoma (GBM) is the most common primary brain tumor and shares characteristics with glial cells. Despite standard treatment using safe maximal resection and chemo-radiotherapy, GBM generally regrows and/or recurs. The mean 5-year survival rate of GBM patients is less than 10% [62, 74], which has not significantly improved in the past several decades.

The resulting tumor mass is easily detected using gadolinium-enhanced T1-weighted images

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(Gd-T1WI) in magnetic resonance imaging (MRI). GBM cells invade white matter and migrate into the contralateral hemisphere through the corpus callosum, even in the early stages of tumor progression [86]. Enhanced tumor lesions are surrounded by edema, where invading GBM cells are detected pathologically. In cases in which enhanced tumor lesions are completely removed by surgical operation and chemo-radiotherapy, GBMs typically recur in the white matter around the tumor removal cavity but are rare in areas distant from the primary lesion [9, 26, 66]. This suggests that glioma stem cells (GSCs) [71] which are responsible for recurrence survive in the tissue just outside of the enhanced lesion [26–28]. Biological characterization of this border area between the brain and tumor mass is essential for inhibiting recurrence and removing GSCs, which may improve the prognosis of patients with GBM. Moreover, although GBM invades the white matter, it does not grow toward the empty cavity after tumor resection. These results suggest that the interaction between GBM cells and non-GBM cells is crucial for tumor invasion and regrowth. Unique microenvironments for GSC niches inside the tumor mass have previously been discussed, but studies investigating the outside of the tumor mass are rare [19, 26, 27, 34, 47, 64, 67, 68]. GBM cells and non-GBM cells, including immune cells, neural cells, and brain vascular cells, along with the extracellular matrix, form the GSC niche at the tumor border [26, 28, 64, 70]. Accumulation of oligodendrocyte progenitor cells (OPCs) and microglia/macrophage at the tumor border contributes to the unique GBM microenvironment, promoting stem like characteristics and chemo-radioresistance [26]. The relationship between GBM and microglia/macrophages has been reported previously [2, 26, 48, 65]. This review focuses on the interesting characteristics of OPCs and their interactions with GBM [26, 28], as well as the novel concept of a "border niche" composed of accumulating oligodendrocyte lineage cells (OLCs) named glioma-associated oligodendrocytes (GAOs).

8.1.1 Cells Residing in the Brain Parenchyma

The central nervous system (CNS) is composed of neurons, glia (astrocytes and oligodendrocytes), and microglia. Neurons, astrocytes, and oligodendrocytes originate from neuroepithelial cells; in contrast, microglia are derived from erythromyeloid progenitors in the yolk sac and migrate into the CNS early during development [23, 32, 76] (Fig. 8.1a). Recently, it had been reported that the human brain contains a glia to neuron ratio of less than 1:1, and the total number of glia is less than 100 billion [83]. Roughly, the glial subtypes in human brains are 20% astrocytes, 3–10% OPCs, 25% oligodendrocytes, and 5–15% microglia, all of which influence nervous system development and maturation [1] (Fig. 8.1b). The most abundant types of glia in the brain are OLCs, including OPCs and mature oligodendrocytes.

8.1.2 GBM Development and Recurrence in the White Matter

Generally, GBM-enhanced mass lesions visualized by Gd-T1WI MRI are located in the white matter, through which GBM extensively invades [86]. Upon recurrence, enhanced mass lesions are identified in the white matter surrounding the empty post-resection cavity [9, 26] (Fig. 8.2a). Complete tumor resection was reported in 43 (48.3%) of 89 newly diagnosed patients with GBM, which was confirmed by Gd-T1WI MRI performed within 72 h after operation. After complete resection and chemo-radiotherapy, recurrence was observed in 30 (69.8%) cases in monthly MRIs during the observation period of

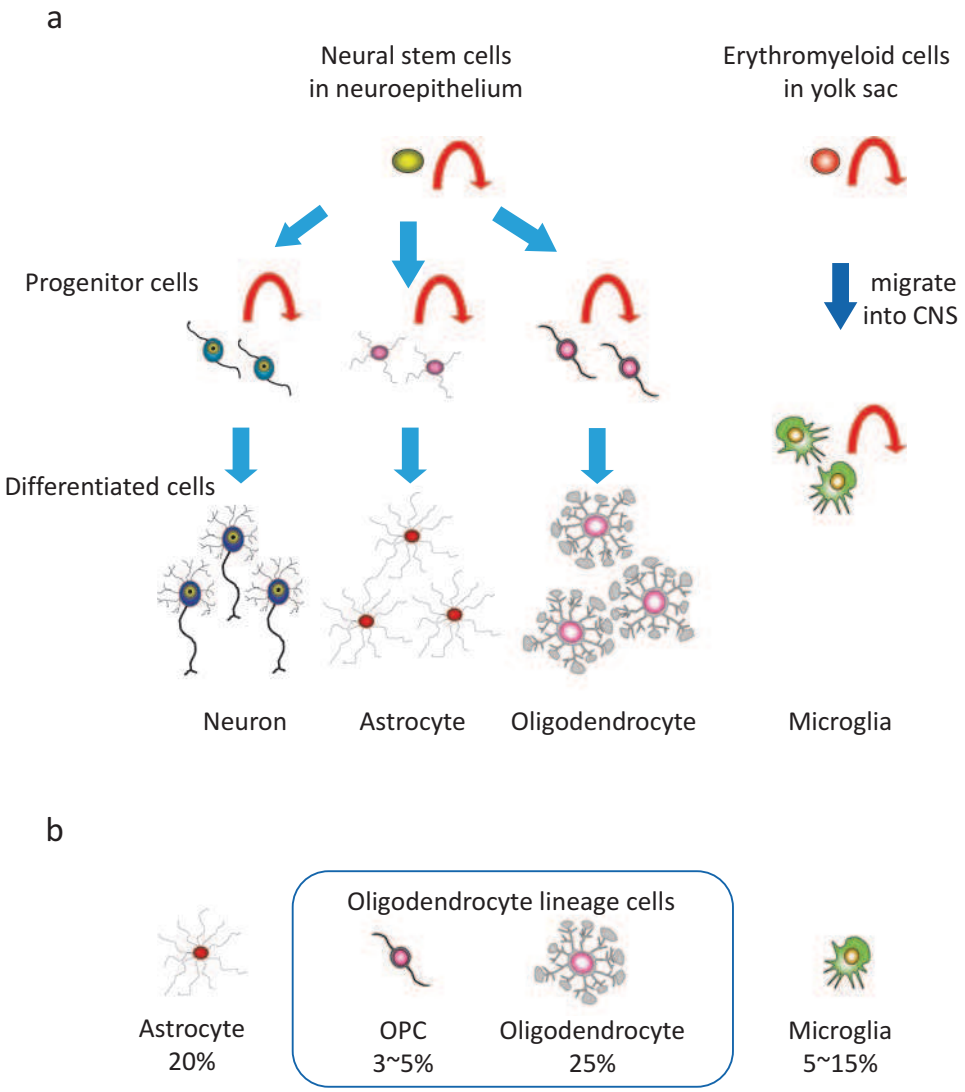

Fig. 8.1 Main cell populations of the brain. (**a**) Neurons, astrocytes, and oligodendrocytes differentiate from NSCs. However, microglia originate from erythromyeloid cells in the yolk sac and migrate into the CNS early during development. (**b**) OLCs are the most abundant cell type in the CNS

1.5–4.5 years post-resection. Primary recurrence was detected in the surrounding white matter in 26 (87%) cases and in the distant white matter in 1 (3%) case; dissemination was visualized in three (10%) cases, but recurrence in the gray matter was not observed [26] (Fig. 8.2b). These results suggest that white matter, but not gray matter, promotes the survival of GBM cells after chemo-radiotherapy. Thus, white matter at tumor borders provides factors that promote therapeutic resistance in GBM cells.

8.2 Change in miRNA Expression at the Tumor Border

To identify molecules at the tumor border involved in chemo-radioresistance and recurrence by promoting stem cell characteristics in GBM, miRNAs were evaluated because of their wide regulation of multiple targets and their secretion into the extracellular space, both which may alter the microenvironment [42, 44, 49].

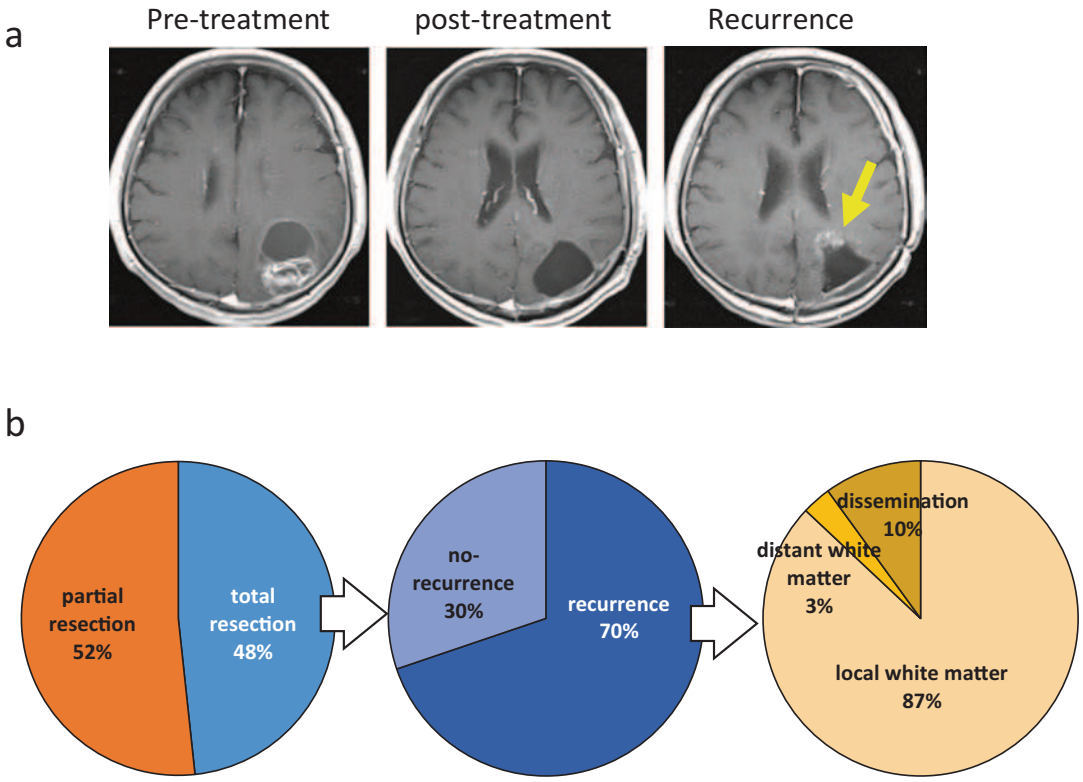

Fig. 8.2 GBM commonly recurs in the white matter. (**a**) Representative case of a patient with GBM post-treatment. Even after complete removal of the enhanced mass lesion and chemo-radiotherapy, recurrence is commonly observed in the white matter around tumor removal cavity (yellow arrow). (**b**) Complete removal of the enhanced mass lesion was achieved in 43 (48.3%) of 89 cases of newly diagnosed patients with GBM. After standard treatment, recurrence was detected in 30 cases (69.8%). Recurrence was seen in the local white matter in 26 cases (87%) and in the distant white matter in 1 case (3%), while dissemination was seen in 3 cases (10%)

To elucidate the features of this tumor border microenvironment, miRNA expression in resected tissue samples was compared from three sites in individual patients with GBM: the tumor mass (tumor), the border between the tumor mass and the brain where glioma and non-glioma cells co-exist (border), and the peripheral area distant from the tumor mass containing normal cells (periphery) (Fig. 8.3a). To obtain microarray data, tissue samples from three sites were divided in half: one half was used for pathological examination and the other half was used for purification of small RNAs if the pathological findings were suitable for downstream analysis [26] (Fig. 8.3b). miRNAs with altered expression were identified at the tumor border (Table 8.1).

8.2.1 Accumulation of Oligodendrocyte Lineage Cells (OLCs) at the Tumor Border

Interestingly, the top three miRNAs (*miR-219-5p*, *miR-219-2-3p*, and *miR-338-3p*) with increased expression at the tumor border play major roles in oligodendrocyte differentiation [3, 16, 17, 60, 89]. In miRNA in situ hybridization, increased *miR-219-5p*-positive cells were observed at the tumor border, but not within tumors. Immunohistochemical staining of the oligodendrocyte lineage markers Olig2, NG2 (also known as chondroitin sulfate proteoglycan 4), O4, and myelin basic protein (MBP) revealed increased

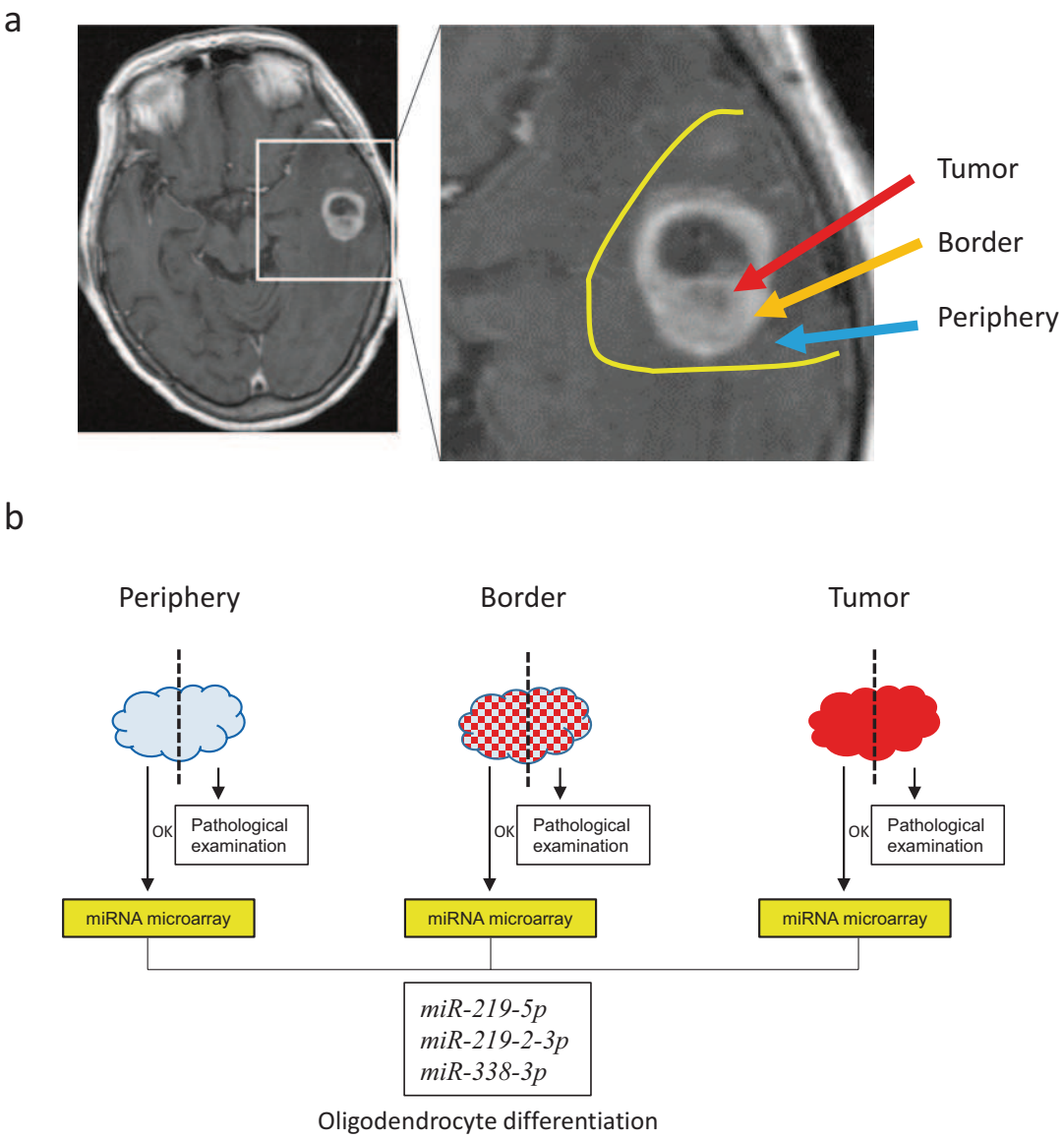

Fig. 8.3 miRNAs showing characteristically higher expression at the tumor border had functions related to oligodendrocyte differentiation. (**a**) The yellow line traces the tumor removal site. After tumor resection, three tissue samples were obtained from three regions (tumor, border, and periphery) and divided into two pieces. (**b**) Half of each piece was used for pathological examination. Pathologically, the tumor was defined as typical GBM tissue, the border as a mixture of tumor and normal cells, and the periphery as nearly normal brain tissue. The other half was used to purify small RNAs after pathological confirmation, and miRNA microarray analysis was done. The top three miRNAs (*miR-219-5p, miR-219-2-3p, and miR-338-3p*) that had increased expression at the tumor border had functions related to oligodendrocyte differentiation

marker-positive cells at the border [7, 26, 60, 85]. Upon pathological examination of 19 cases of newly diagnosed GBM samples containing the tumor border, abundant Olig2-positive cells within the tumor were found in ten (52.6%) cases but rarely in 9 (47.4%) cases [26]. In contrast, all cases showed accumulation of Olig2-positive cells at the tumor border [26]. NG2, O4, and

Table 8.1 miRNAs showing characteristically higher expression at the tumor border

miRNA	Periphery	Border	Tumor
Hsa-miR-219-5p	5.187	8.062	1
Hsa-miR-219-2-3p	5.845	8.037	1
Hsa-miR-338-3p	4.562	6.492	1
Hsa-miR-27b	1.491	2.176	1
Hsa-miR-23b	1.545	2.041	1

MBP were also detected at the border. These data suggest that OLCs, including OPCs, accumulate abundantly at the tumor border. However, accumulation of OLCs was only observed at sites where individual GBM cells invaded into the white matter, but not at the clear interface between the tumor and brain [26] (Fig. 8.4a).

8.2.2 Soluble Factors Secreted by OPCs Induce Stemness and Chemo-Radioresistance in GBM Cells

To investigate how OPCs interact with GBM cells, conditioned medium (CM) was prepared from the human A172 and T98G GBM cell lines (CM-A172 and CM-T98G), macrophages (CM-Mac), OPCs (CM-OPC), and OPCs plus macrophages (CM-OM). Interestingly, cell viability of OPCs was increased in medium containing CM-A172, CM-T98G, and CM-Mac [26]. This suggests that factors secreted from GBM cells directly affect the proliferation potential of normal OPCs (Fig. 8.4b). Further, addition of CM-OPC in the culture medium induced significantly higher expression of stemness genes *Nanog*, *Sox2*, aldehyde dehydrogenase isoform 1 (*ALDH1*), *Oct3/4*, and *Bmi1* and increased the sphere formation and cell viability of A172 cells [26]. Expression of ATP-binding cassette subfamily G member 2 (*ABCG2*), which plays a role in drug efflux, was significantly elevated in A172 cells cultured with CM-OPC. Addition of CM-OPC into the culture medium also increased the cell viability of A172 cells after treatment with temozolomide, the standard chemotherapy for GBM. Moreover, phosphorylated signal transducer and activator of transcription 3 (pSTAT3), which is important for radioresistance and stemness [36, 39, 43], was increased in A172 cells cultured with CM-OPC [26]. Thus, OPCs play an important role in GBM stemness and chemo-radioresistance [26] (Fig. 8.4b).

Moreover, DNA microarray analysis of OPCs and macrophages revealed increased expression of FGF1 and EGF in OPCs compared to in macrophages, and addition of FGF1 and EGF in the culture medium increased sphere formation and cell viability of GBM cells [26] (Fig. 8.4b). Recently, Kawashima et al. reported that CM-oligodendrocytes, established from human glioma tissue (WHO Grade II), increase the migration and invasion of GBM cells, in contrast to CM-fibroblasts established from GBM [41]. The authors concluded that these functions are regulated by angiopoietin-2 signaling [41] (Fig. 8.4b).

8.3 "Border Niche": A Novel Concept in GBM Characterized by Accumulation of OLCs

The perinecrotic niche (hypoxic niche) and perivascular niche within the tumor mass have been well studied to understand the mechanisms of stemness and chemo-radioresistance [11, 14, 31, 67, 68]. Despite complete removal of the enhanced mass lesion in Gd-T1WI, which removes these niches along with the tumor mass, recurrence commonly occurs in the white matter around the tumor removal cavity. At this site, OLCs including OPCs tend to accumulate, which promotes stemness and chemo-radioresistance in GBM cells. We defined this unique microenvironment outside of the tumor mass containing abundant OPCs as the "border niche," which promotes the survival and recurrence of GBM cells. This novel border niche is a new target of research and treatment [26, 28] (Fig. 8.4a).

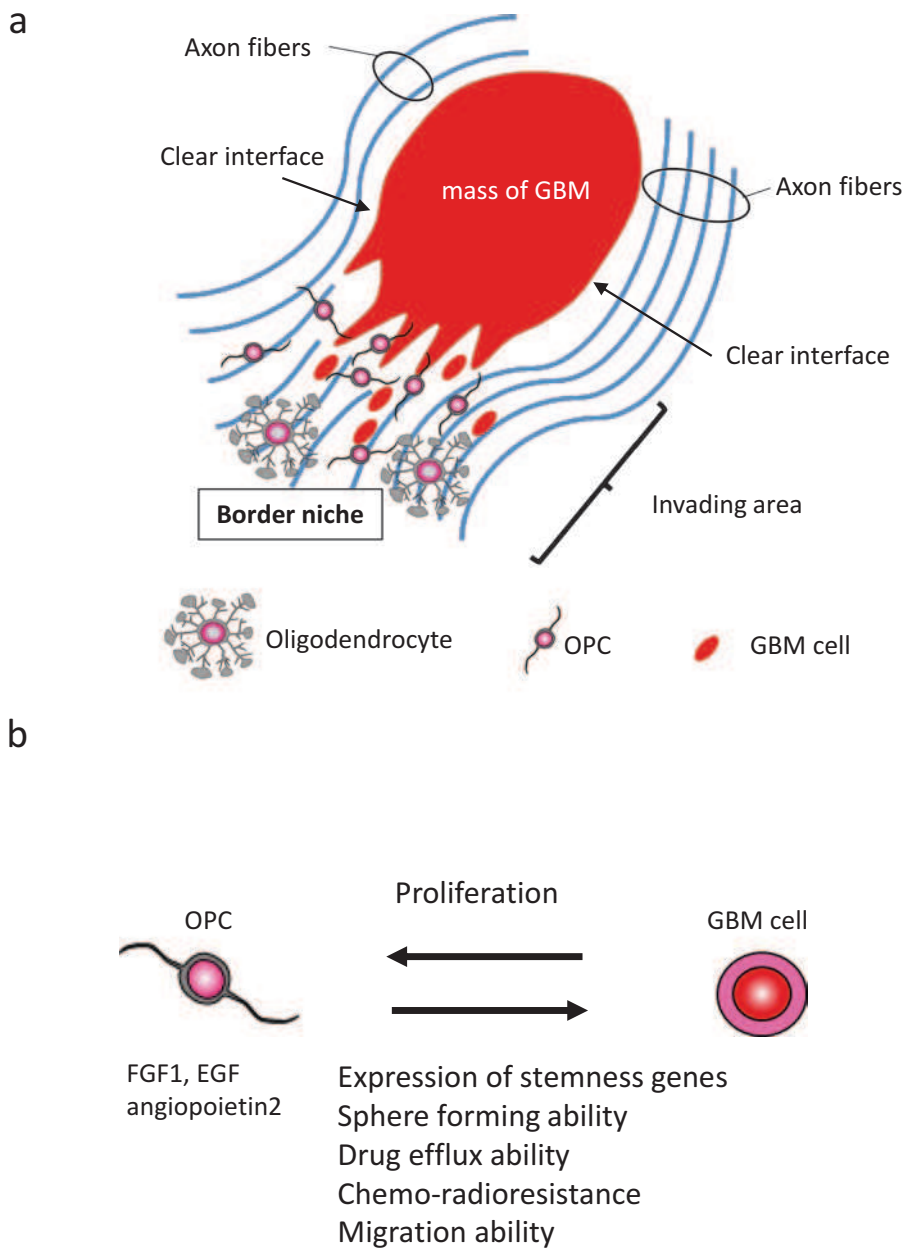

Fig. 8.4 OLCs, including OPCs, accumulate in the invading area. (**a**) Pathologically, the border between the tumor and brain was divided into two types: invading and clear interface areas. OLCs, including OPCs, accumulate in the invading area and form border niche with GBM cells. However, OLCs were not increased in the area showing clear interface. (**b**) GBM cells induce proliferation of OPCs. On the other hand, OPCs induce GBM cells with stem cell-like characteristics

8.3.1 OPCs Are Key Players in the Development and Invasion of GBM

OPCs are an important cell type in GBM and have been reported as the cells of origin for this tumor [21, 30, 51, 75]. Previously, we established artificial glioma-forming cells by overexpressing an active form of HRas in neural stem cells (NSCs), OPCs, and astrocytes isolated from the p53 knockout mouse. Interestingly, GBMs formed in the brains of nude mice after orthotopic injection of as few as ten cells from the NSC or OPC lines. However, cells originating from astrocytes required injections of 10,000 cells to form anaplastic astrocytoma, but never formed GBM. These results demonstrated that NSCs and OPCs have a similar potential to be the GBM cell of origin [29, 30].

Generally, rapid extension of GBM into the white matter, which is abundant in neurons and OLCs, is detected in Gd-T1WI MRI. One of the characteristic growth patterns associated with GBM is a butterfly shape due to invasion of GBM into the contralateral hemisphere through commissure fibers in the corpus callosum. Other patterns of extension are along the radiation of the corpus callosum, association fibers, or arcuate fasciculus in the bilateral hemispheres, and these patterns do not coincide with the vascular network. Because the axons are myelinated with oligodendrocytes, this location contains abundant proliferating OPCs [28]. Thus, GBM cells preferentially use myelinated axon fibers as a scaffold to migrate to and colonize additional tissue and construct the border niche to acquire stemness and therapeutic resistance [26, 28]. However, differentiated neurons cannot proliferate; therefore, GBM cells manipulate OPCs to form a tumor-supportive niche via the dynamic functions of OPCs in migration and proliferation. OPCs can promote the development, progression, invasion, resistance, and recurrence of GBM.

8.3.2 OPCs Dynamically Proliferate and Differentiate in Healthy Brains

Myelin, produced by differentiated oligodendrocytes, is a critical component of the vertebrate CNS. This myelination of axons regulates neuronal activities, mediates neural plasticity, and provides metabolic support [5, 20, 38]. Generally, the rate of myelin turnover is high, whereas the oligodendrocyte population itself is remarkably stable in the white matter [87]. Myelination and remyelination continue to occur throughout life [46]. OPCs constitute the majority of proliferating cells in the adult brain and exhibit specific characteristics, individual OPCs occupy their own territory, and OPC density is maintained through local proliferation. OPCs migrate rapidly to sites of injury [33] and are known to occupy regions of traumatic brain injury within one day post-injury [15]. Furthermore, they migrate and proliferate faster than astrocytes [18]. Neuronal activity also rapidly remodels white matter; for example, exercise stimulates OPC proliferation and oligodendrocyte differentiation within a few days [56].

Optogenetic, electrical, and pharmacogenetic stimulation of neurons induces oligodendrogenesis and myelination [22, 50, 58]. The selection of axons for myelination is strongly influenced by the relative activity of individual axons within a population [58]. In line with this observation, Bergles et al. reported that OPCs receive synaptic inputs from neurons [6], and neuron-oligodendroglial communication is mediated by glutamate and GABA in the CNS [25, 45].

However, not all axons are myelinated within the white matter tracts. For example, the proportion of unmyelinated fibers within the corpus callosum was relatively constant across species, with approximately 30% of fibers lacking myelination within the corpus callosum [61]. A study of the myelin distribution along single axons of pyramidal neurons revealed the distinct longitudinal distribution of myelin of individual

neurons [77]. Myelination does not peak in the human brain until the fifth decade, which then decreases rapidly starting at 60 years of age [52, 53]. Interestingly, decline in the ability of OPCs to myelinate axons coincides with the age most liable to develop GBM.

8.3.3 Heterogeneity of OPCs

OPCs exist in the various sites of the brain; however, their functional differences in these regions have not been well studied. OPCs in forebrain white matter (corpus callosum) have a shorter cell cycle (completed in ~10 days) than those in gray matter (motor cortex: ~36 days) of the mouse brain 60 days after birth [88]. Moreover, transplantation experiments revealed that OPCs from white matter differentiate into mature, myelinated oligodendrocytes preferentially in white matter compared to in gray matter, whereas gray matter-derived OPCs do so less efficiently [82]. Interestingly, OLCs have been classified into 13 populations with region- and age-specific distributions according to single-cell RNA sequencing data from 5072 cells [55], and Spitzer et al. reported that OPCs become regionally diverse and heterogeneous with age [73].

8.4 Other Supportive Cells

Several non-tumor cells, including microglia, macrophages, astrocytes, pericytes, and T cells, have been reported to play a pivotal role in promoting the proliferation, migration, and recurrence of GBM [11, 14, 67, 68]. Recently, it was reported that reciprocal signaling between GSCs and differentiated glioma cells promotes malignant progression [84].

8.4.1 Differentiated Glioma Cells

Differentiated glioblastoma cells (DGCs) express brain-derived neurotrophic factor (BDNF), whereas GSCs express the BDNF receptor NTRK2. DGCs communicate with GSCs through BDNF-NTRK2-VGF paracrine signaling to promote growth [84]. However, the microenvironments that foster this communication are within the tumor, not at the border, suggesting that DGCs have an important supportive function for GBM cells inside the tumor mass, but not at the border niche. Because DGCs do not seem to proliferate and migrate rapidly, they cannot quickly modulate the microenvironment at the border niche.

8.4.2 Microglia

From the perspective of oligodendrogenesis and myelination, microglia-derived factors can influence OLC chemoattraction, proliferation, differentiation, and myelination/remyelination. Moreover, microglia enhance the differentiation of neural stem/progenitor cells into OLCs [10, 57, 69]. In GBM tissue, bone marrow-derived macrophages are prominent in the perivascular areas, whereas resident microglia are present in high numbers in the peritumoral region [12, 13]. Because the border niche exists in the peritumoral region where abnormal vessels have not yet developed sufficiently, microglia constitute the majority of glioma-associated microglia/macrophages at the border. Further investigation into the interaction between OPCs and microglia is needed to reveal the mechanisms of the border niche in GBM progression and recurrence [28].

8.4.3 Astrocytes

The identity of astrocyte lineage cells remains unclear. Interestingly, subpopulations of healthy astrocytes in the adult brain and their glioma counterparts are endowed with diverse cellular, molecular, and functional properties. Further, some populations contribute to synaptogenesis and tumor pathophysiology [37]. Astrocytes in the tumor microenvironment promote the proliferation, migration, and therapeutic resistance of GBM cells [8, 24]. Interestingly, glioma-associated astrocytes (tumor-associated astro-

cytes) show a different miRNA expression profile from normal astrocytes [40]. Based on the supportive function of oligodendrogenesis, astrocytes affect the proliferation and remyelination of OPCs [54, 59] and therefore play indirect roles in forming the border niche. Astrocytes have a low proliferation rate and low migration potential to sites of wound injury [4], whereas OPCs and microglia play an immediate role in CNS injury [18]. These data suggest that OPCs and microglia play a more critical role in border niche formation than astrocytes [26, 28].

8.4.4 Neurons

Neuronal activity not only affects the migration and proliferation of OPCs [20, 22, 50, 58] but also promotes the survival of GBM cells directly. Neuronal regulation of glioma is dependent on the cleavage and secretion of the synaptic adhesion molecule neuroligin-3, which promotes glioma proliferation through the PI3K-mTOR pathway [79, 81] (Fig. 8.5a).

Seizure is one of the accompanying symptoms in patients with glioma. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-type glutamate receptors (AMPARs) mediate neurotransmission in excitatory synapses and are expressed not only in neuron and glia cells but also in GBM cells [35]. Inactivation of AMPARs suppresses migration and induces apoptosis in glioma cells [35] (Fig. 8.5b).

Moreover, some GBM cells form synapses with neurons, and then synaptic and electrical integration into neural circuits promotes glioma progression [80]. Recently, perampanel (AMPAR inhibitor) was used as an anticonvulsant. In in vivo experiments, an approximately 50% decrease in glioma proliferation was observed in perampanel-treated mice compared to in vehicle-treated control mice [80]. Additionally, glutamatergic synaptic input to glioma cells drives the progression of glioma, and blockade of neuro-gliomal synapses-driven synaptic communication between neurons and GBM cells via genetic and pharmacological blockade of AMPAR signaling reduced GBM cell malignancy, leading to attenuated glioma progression [78]. Thus, these results showing direct interactions between neurons and GBM cells provide insight into progression and niche formation in GBM (Fig. 8.5a, b).

8.5 Further Perspective

Neuronal activity promotes the progression of GBM and proliferation of OPCs [22, 50, 58, 78, 80]. However, various aspects of this process remain unresolved. The soma of the neuron is located in the gray matter and the axon in the white matter. Generally, synapses exist in the gray matter. OPCs in the white matter show a higher potential for proliferation than those in the gray matter [55, 73, 82, 88]. However, GBM develops and recurs in the white matter. In the white matter, neurons, GBM cells, and OPCs may interact directly in a synaptic and non-synaptic manner, or intervention of OPCs between neuron and GBM cells occurs to promote the progression of GBM. Further studies are needed to reveal the mechanisms of invasion, proliferation, chemo-radioresistance, and recurrence of GBM (Fig. 8.6).

8.6 Conclusion

The ultimate goal of GBM treatment is to completely abolish GBM cells. Standard treatment for patients with GBM is maximal safe resection and chemo-radiotherapy to inhibit recurrence and dissemination. GBM cells rapidly accumulate mutations, making the tumor highly heterogeneous [63, 72]. The application of therapies targeting not only GBM cells but also non-glioma cells, OPCs, neurons, microglia, and other cells that form the border niche will contribute to better prognosis [26, 28] (Fig. 8.6).

Further studies of the border niche may provide insight into fundamental processes such as the development, progression, migration, and recurrence of GBM and may be useful for preventing recurrence in patients.

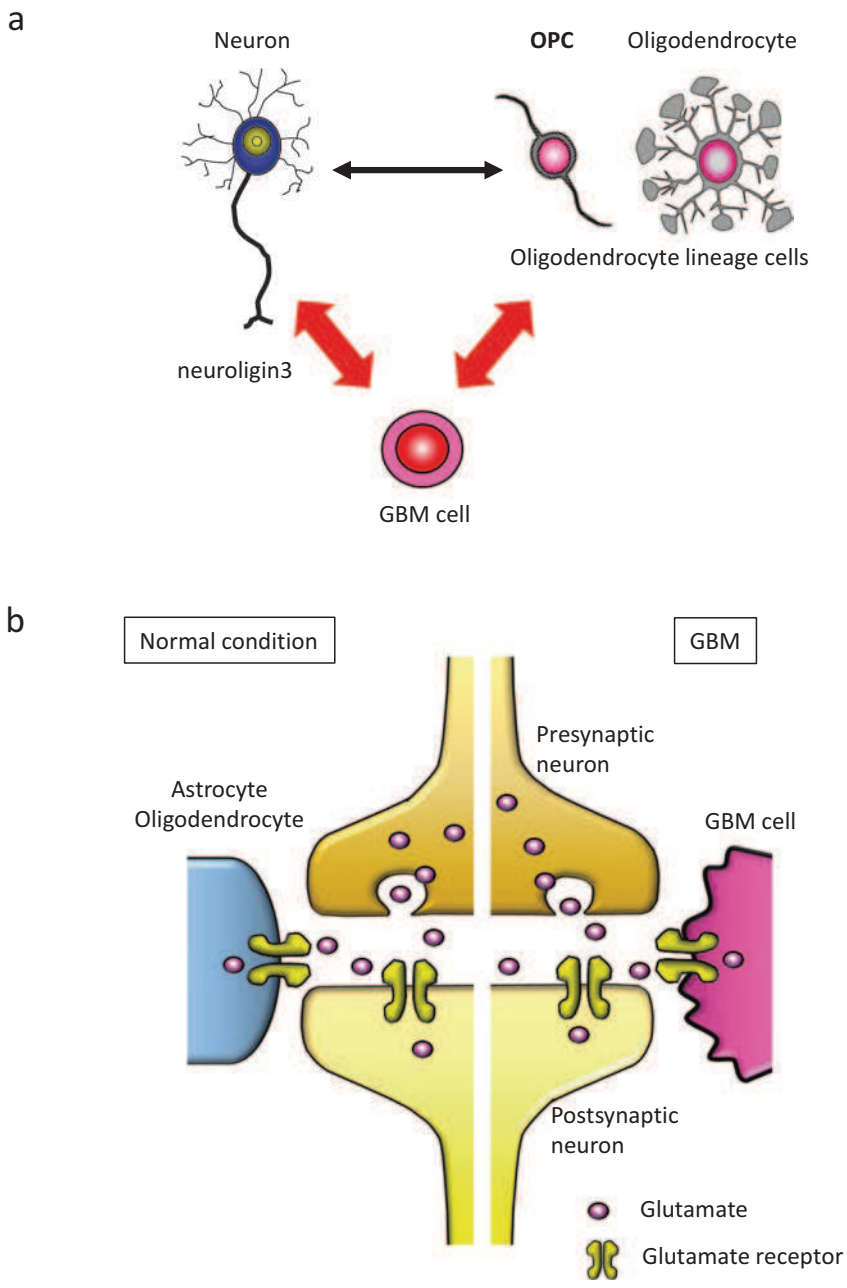

Fig. 8.5 Neurons interact with glial cells and GBM cells. (**a**) Neurons interact closely and dynamically with OLCs, including OPCs. The direct interaction between neurons and GBM cells has recently been discussed. Understanding the mechanisms of interaction among neurons, OPCs, and GBM cells is crucial for improving the prognosis of GBM patients. (**b**) Glutamate receptors are expressed on neurons, astrocytes, oligodendrocyte, and GBM cells. Signals from neurons promote proliferation and migration of GBM cells

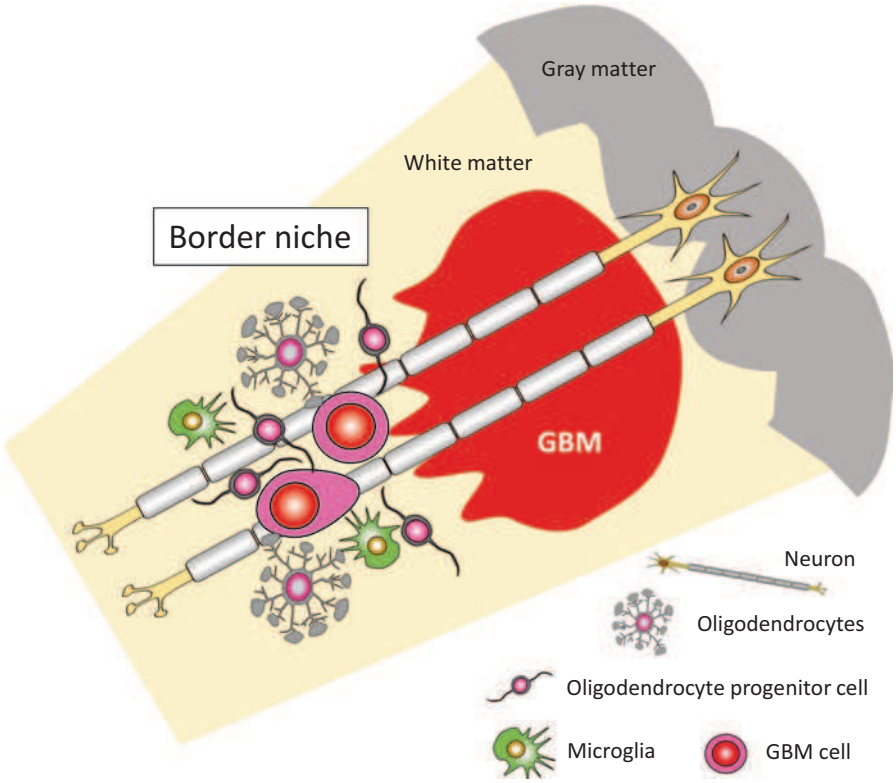

Fig. 8.6 Border niche in GBM. In the border niche, crosstalk between GBM cells and non-GBM cells, OPCs, and microglia promotes stemness and therapeutic resistance in GBM cells. Neuronal activity induces proliferation of both OPCs and GBM cells. GBM cells prefer to migrate within the fasciculus of axons where abundant OLCs, including OPCs, exist, particularly at the border. The border niche is characterized by GAOs

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