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REVIEW ARTICLE

Novel concept of the border niche: glioblastoma cells use oligodendrocytes progenitor cells (GAOs) and microglia to acquire stem cell-like features

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Abstract
Glioblastoma (GBM) is a major malignant brain tumor developing in adult brain white matter, characterized by rapid growth and invasion. GBM cells spread into the contralateral hemisphere, even during early tumor development. However, after complete resection of tumor mass, GBM commonly recurs around the tumor removal cavity, suggesting that a microenvironment at the tumor border provides chemo-radioresistance to GBM cells. Thus, clarification of the tumor border microenvironment is critical for improving prognosis in GBM patients. MicroRNA (miRNA) expression in samples from the tumor, tumor border, and peripheral region far from tumor mass was compared, and five miRNAs showing characteristically higher expression in the tumor border were identified, with the top three related to oligodendrocyte differentiation. Pathologically, oligodendrocyte lineage cells increased in the border, but were rare in tumors. Macrophages/microglia also colocalized in the border area. Medium cultured with oligodendrocyte progenitor cells (OPCs) and macrophages induced stemness and chemo-radioresistance in GBM cells, suggesting that OPCs and macrophages/microglia constitute a special microenvironment for GBM cells at the tumor border. The supportive function of OPCs for GBM cells has not been discussed previously. OPCs are indispensable for GBM cells to establish special niches for chemo-radioresistance outside the tumor mass.

Keywords Oligodendrocyte progenitor cell · Microglia · Border niche · Microenvironment · Glioblastoma

Introduction

Glioblastoma (GBM) is a lethal tumor that occurs in the adult brain white matter. It expands rapidly and invades into the white matter extensively. Following standard treatment, namely, safe maximal resection and chemo-radiotherapy, GBM generally shows regrowth and recurrence, and patients have a mean 5-year survival rate of less than 10% [1, 2]. This indicates that treatment of GBM patients is not yet satisfactory.

GBM cells invade the brain's white matter and extend into the contralateral hemisphere through the corpus callosum during the early stage of tumor development [3]. The resultant tumor mass can easily be detected in gadolinium-enhanced T1-weighed images (Gd-T1WI) from magnetic resonance imaging (MRI). Tumors are surrounded by large edema in white matter, where invading GBM cells are detected pathologically. In cases, where enhanced mass lesions are completely removed by surgical operation, followed by chemo-radiotherapy, GBMs usually recur in the white matter around the tumor removal cavity, but are rare in areas distant from the primary lesion [4–6]. This suggests that glioma stem cells (GSCs) [7], which are responsible for recurrence, survive in the tissue just outside of the enhanced lesion [6, 8]. Special intratumoral microenvironments for GSCs (GSC niches) have been discussed previously, but information concerning microenvironments outside of tumor masses is rare [6, 8–15]. Glioma cells as well as non-glioma cells, including immune cells, neural cells, and brain vascular cells, along with the extracellular matrix, are essential for GSC niche formation [12, 16]. We previously reported that oligodendrocyte progenitor cells (OPCs) and macrophages/microglia accumulating at the tumor border modulate particular microenvironments for GBM cells, promoting stem-cell-like characters and chemo-radioresistance [6].

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We proposed that these special microenvironments, which characterize accumulated OPCs, be termed "border niches" and that the oligodendrocyte lineage cells be termed glioma-associated oligodendrocytes (GAOs) [6]. The relationships between GBM cells and microglia/macrophages have been reported previously [17–19]. Therefore, in this review, we mainly discuss this novel concept of "border niche" and important functions of OPCs in chemo-radioresistance, migration, and recurrence of GBM.

Characteristics of GBM development and recurrence

GBM cells invade white matter extensively [3]. A previous study reported that approximately 78.5% of recurrent GBMs were found around the primary lesion (inside and at the margin of the radiation field: 72.2% and 6.3%, respectively) [4]. In our data, complete resection was performed in 43 (48.3%) of 89 newly diagnosed patients with GBM, which was confirmed in Gd-T1WI performed within 72 h after operation. In the analysis of 30 (69.8%) recurrent cases in the complete resection group, 26 cases (87%) involved primary recurrence within the white matter attached to the tumor removal cavity identified in the monthly repeated MRI (Fig. 1a) [6]. These results suggest that while GBM cells are widely distributed in white matter, recurrence is commonly seen at the tumor border. The white matter just around the tumor mass constitutes a hotbed for GBM recurrence (Fig. 1b). Thus, GBM cells at tumor borders acquire therapeutic resistance.

Characteristics of the microenvironment at the tumor border

We hypothesized that some molecules at the tumor–brain interface (the border area) may enhance chemo-radioresistance and recurrence by promoting stem cell characteristics in GBM cells. We focused on microRNAs (miRNAs) because of their unique features, which include regulation of multiple targets, secretion into the extracellular space, and their function as conveyors of information between tumor cells and the tumor microenvironment [20–23].

To elucidate the features of this unique microenvironment, we compared miRNA expression in samples from three sites in resected tissue from individual patients with GBM: the tumor mass (tumor); the border area between the tumor mass and brain, where glioma and non-glioma cells

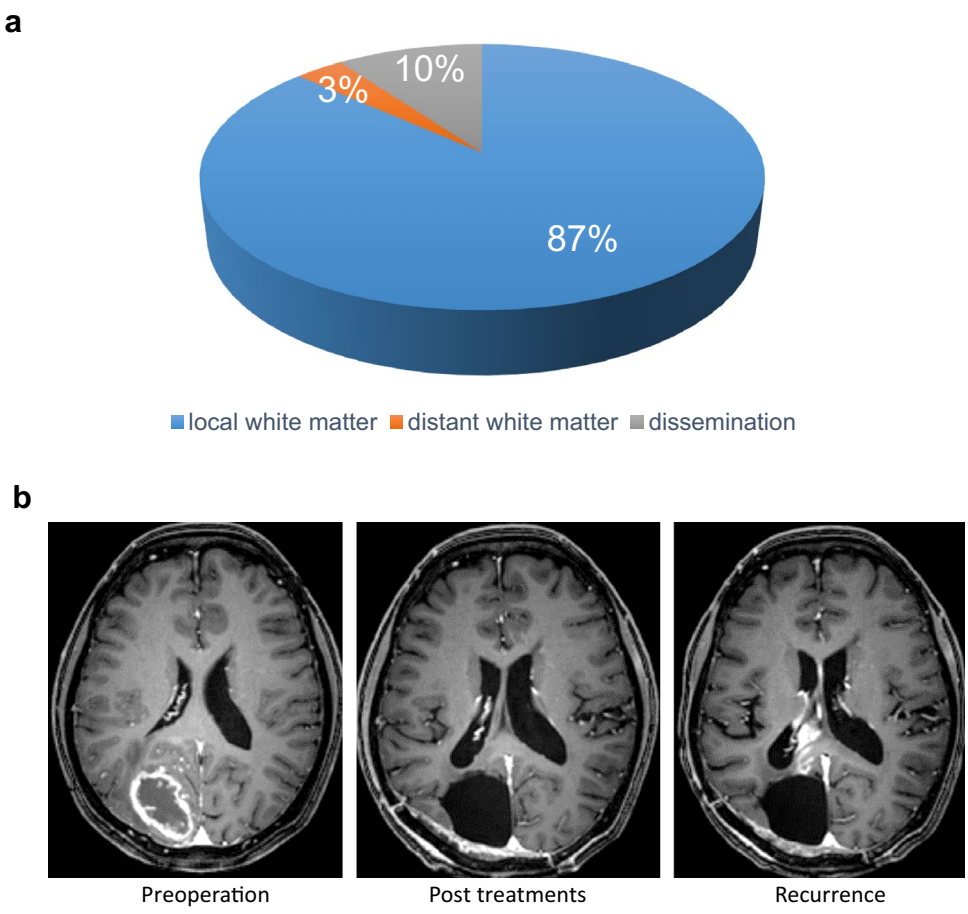


Fig. 1 GBM recurs in local white matter. **a** Complete removal was defined as removal of a single enhanced mass lesion. In most cases, local recurrence was observed in the white matter at the edge of the tumor removal cavity (26 cases; 87%). Three cases (10%) of subarachnoid dissemination were identified, but only one case (3%) showed distant recurrence in the white matter. There was no recurrence in gray matter in this series. **b** Even though complete removal was confirmed by MRI, GBM commonly recurred in the white matter surrounding the tumor removal cavity

co-exist (border); and the peripheral area far from the tumor mass containing mostly normal cells (periphery) (Fig. 2a). Fortunately, we identified miRNAs displaying characteristic changes in expression level at the tumor border.

Oligodendrocyte lineage cells are increased in the border

Interestingly, the three miRNAs (*miR-219-5p*, *miR-219-2-3p*, and *miR-338-3p*) showing the highest levels of expression in the border area were related to oligodendrocyte differentiation [24–27]. Increased numbers of *miR-219-5p*-positive cells were observed in border areas, but not in tumors. Immunohistochemical staining of oligodendrocyte lineage markers, namely, Olig2, NG2 (also known as chondroitin sulfate proteoglycan 4), O4, and myelin basic protein (MBP), consistently found increased number of marker-positive cells in the border area (Fig. 2b) [27–29]. These data suggest that oligodendrocyte lineage cells (OLCs), including OPCs, characteristically accumulated at tumor border areas. However, accumulation of OLCs was only seen at sites, where individual GBM cells started to invade into white matter and not at the clear interface between tumor and brain.

Macrophages/microglia are attracted to the tumor and border

The miRNA present at the highest level, *miR-219-5p*, also possesses anti-apoptotic function in macrophages [30]. It had been reported that macrophages/microglia infiltrate GBM tissues in large numbers [31–35]. However, the numbers of Iba1$^+$ and CD163$^+$ macrophages were found to be increased not only in the tumor, but also in

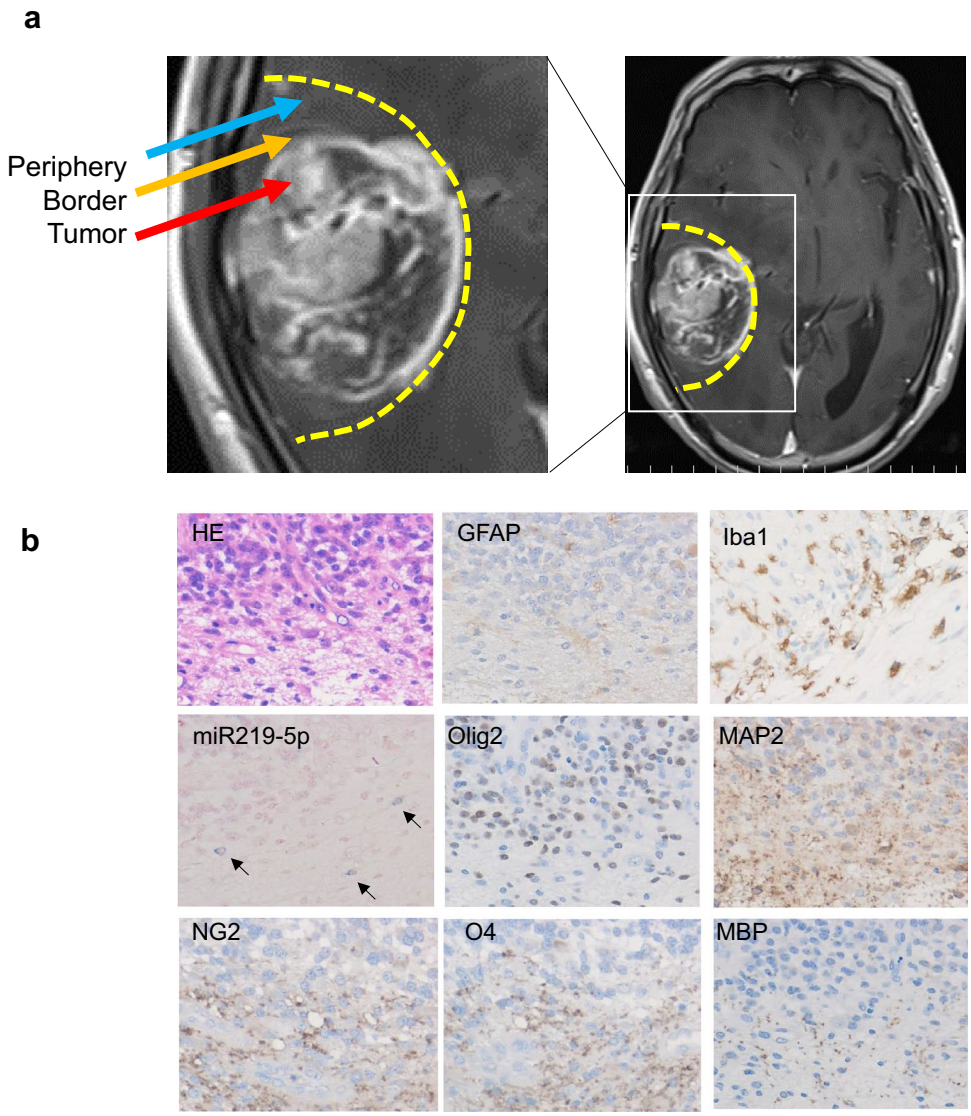


Fig. 2 Oligodendrocyte lineage cells increased in the border area. **a** Three tissue samples were obtained from three regions (tumor, border, and periphery). The yellow broken line shows the area of resection. **b** In situ hybridization identified *miRNA-219-5p* positive cells in the border area. GFAP and Iba1 positive cells were seen in both the tumor and the border. Immunoreactive oligodendrocyte lineage markers (Olig2, NG2, O4, and MBP) were found in the border area

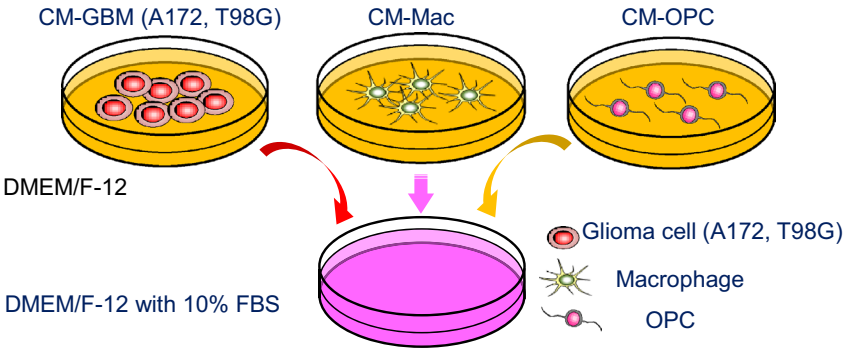
border areas. In addition, $NG2^+$ OPCs were found to co-localize with $Iba1^+$ macrophages/microglia in the border area of GBM tissue. GFAP-positive tumor cells were seen in tumors, as well as in the tumor border and periphery, so it was difficult to discern any characteristic localization pattern at the tumor border. Abnormal vessels were identified in the tumor, but did not always appear in the border area. These results suggested that OPCs and macrophages/microglia are more important for the construction of special environments in which GBM cells can survive at the border area.

Interaction with OPCs, macrophage, and GBM cells

Soluble factors secreted from OPCs and macrophages increase stem cell-like properties in GBM cells

To investigate how OPCs, macrophages, and GBM cells interacted, we prepared conditioned medium (CM) from human A172 or T98G GBM cell lines (CM-GBM), macrophages (CM-Mac), OPCs (CM-OPC), and OPCs plus macrophages (CM-OM) (Fig. 3a). OPC cell viability was up-regulated in the medium containing CM-GBM and CM-Mac. This novel finding indicated that some secreted molecules derived from

a



b

Target cells	Function	Condition medium CM-GBM	CM-Mac	CM-OPC	CM-OM
OPC	Cell viability	↑	↑	n.p.	n.p.
Macrophages	Invasion	↑	↑	↑	n.p.
GBM (A172,T98G)	Stemness genes	n.p.	↑	↑	n.p.
GBM (A172,T98G)	Cell viability	n.p.	↑	↑	↑
GBM (A172,T98G)	Sphere formation	n.p.	↑	↑	↑
GBM (A172,T98G)	Drug efflux	n.p.	↑	↑	↑
GBM cells (A172)	Chemoresistance	n.p.	-	↑	↑
GBM cells (A172)	Radoresistance	n.p.	-	↑	↑

↑: increased, -: no change, n.p.: not performed

Fig. 3 Conditioned medium derived from OPCs and macrophages induced stem cell-like properties in GBM cells. **a** Condition medium (CM) cultured A172 or T98G GBM cell lines (CM-GBM), macrophages (CM-Mac), and OPCs (CM-OPC) were prepared. OPCs, macrophages, and GBM cells were cultured in medium and supplemented with CM-GBM, CM-Mac, and CM-OPC. Detailed information is provided in original article [6]. **b** Crosstalk between GBM cells, macrophages, and OPCs was identified. Especially, CM-Mac, CM-OPC, and CM-OM (CM-OPC plus macrophages) promoted expression of stemness genes, cell viability, sphere-forming ability, and drug efflux ability in A172 and T98G. Chemoresistance and radioresistance were confirmed in A172 cells

GBM cells affect the proliferation potential of normal OPCs (Fig. 3b). Next, to analyze how OPCs and macrophages modulate GBM cells, real-time polymerase chain reaction (PCR) of some stemness genes was performed. CM-Mac and CM-OPC induced significantly higher expression of the stemness genes *Nanog*, *Sox2*, aldehyde dehydrogenase isoform 1 (*ALDH1*), *Oct3/4*, and *Bmi1*. Moreover, sphere-forming ability and cell viability in GBM cells was significantly up-regulated (Fig. 3b) [6].

GBM cells acquire chemo-radioresistant features from the interaction with OPCs and macrophages

Next, to investigate whether GBM cells acquire chemo-radioresistant ability, we analyzed expression of ATP-binding cassette sub-family G member 2 (*ABCG2*), which plays a role in drug efflux. Analysis by real-time PCR revealed that ABCG2 expression was significantly elevated in GBM cells cultured with CM-Mac, CM-OPC, and CM-OM. To confirm chemoresistant ability, GBM cells (A172) were treated with TMZ, a standard therapeutic drug for GBM. By addition of CM-OPC and CM-OM, the cell viability of A172 was recovered (Fig. 3b). Moreover, levels of phosphorylated signal transducer and activator of transcription 3 (pSTAT3), which is important for radioresistance, and stemness [36–38], were increased in A172 cells cultured with CM-OPC and CM-OM. These data indicated that chemo-radioresistance of GBM cells could be promoted by interaction with OPCs and macrophages [6].

FGF1 and EGF expressed in OPC, and HB-EGF and IL-1β secreted from macrophages up-regulate sphere-forming ability and cell viability in GBM cells

Next, to identify soluble factors that promote stemness profiles in GBM cells, DNA microarray analysis was performed. Some candidate genes including growth factors and cytokines, that were displayed higher and differential expression patterns in OPCs and macrophages were selected. Sphere numbers and cell viability were up-regulated after culturing with FGF1 and EGF, which showed higher expression in OPC, and HB-EGF and IL-1β secreted from macrophages [6].

Taken together, increased numbers of non-tumor cell, OPCs, and macrophages/microglia form special microenvironments, while some molecules secreted from them in the tumor border area promote stem cell-like profiles and therapeutic resistance in GBM cells.

Novel concept of border niche

The perinecrotic niche (hypoxic niche) and perivascular niche in the tumor mass has been well described [13, 14, 39–41]. The concept of such niches is critical for understanding mechanisms of chemo-radioresistance and heterogeneity of GBM. Despite the complete removal of enhanced mass lesion of GBM in Gd-T1WI, initial recurrence is commonly identified in the white matter around the tumor removal cavity, where OLCs including OPCs and macrophages/microglia characteristically accumulate. These special microenvironments outside of the tumor mass are characterized by the existence of OPCs and are critical for local recurrence, so we proposed that such niches be termed "border niches" (Fig. 4) [6, 8].

Oligodendrocyte lineage cells in GBM invasion and recurrence

Oligodendrocytes play several important roles in the brain, where they regulate neuronal activities, mediate neural plasticity, and modulate metabolic support to axons by myelination [42, 43]. In general, myelin is exchanged at a high rate, whereas the oligodendrocyte population itself is remarkably stable in the white matter of humans [44].

During GBM development, an extensive and rapid migration of cells into white matter is seen. One of the characteristic growth patterns associated with GBM is a butterfly shape, indicating that GBM cells invade into the contralateral hemisphere through commissure fibers in the corpus callosum (Fig. 5a, b). Other patterns of extension are along the radiation of the corpus callosum (Fig. 5c) and to association fibers, arcuate fasciculus in the bilateral hemispheres (Fig. 5d). In cases of occurrence in the core of the brain, GBM develops along the superior occipitofrontal fasciculus, superior longitudinal fasciculus, and corpus callosum (Fig. 5e, f), These extension patterns do not always coincide with the vascular network. After total resection of enhanced mass lesions, GBM recurs and extends into the white matter, and does not display an exophytic growth pattern toward the removal cavity.

These results suggested that GBM cells spread preferentially along fasciculus axons which are myelinated with oligodendrocytes, where abundant OPCs exist and proliferate. GBM cells use myelinated axon fibers as tracks and scaffold to form new sanctuaries, which allow them to resist therapeutics. OPCs have been reported as cells of origin for GBM [45–48]. However, the potential of OPCs to supply supportive function to GBM cells has not been previously described.

Proliferation potential of OPCs in non-tumoral condition

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. Especially, OPCs

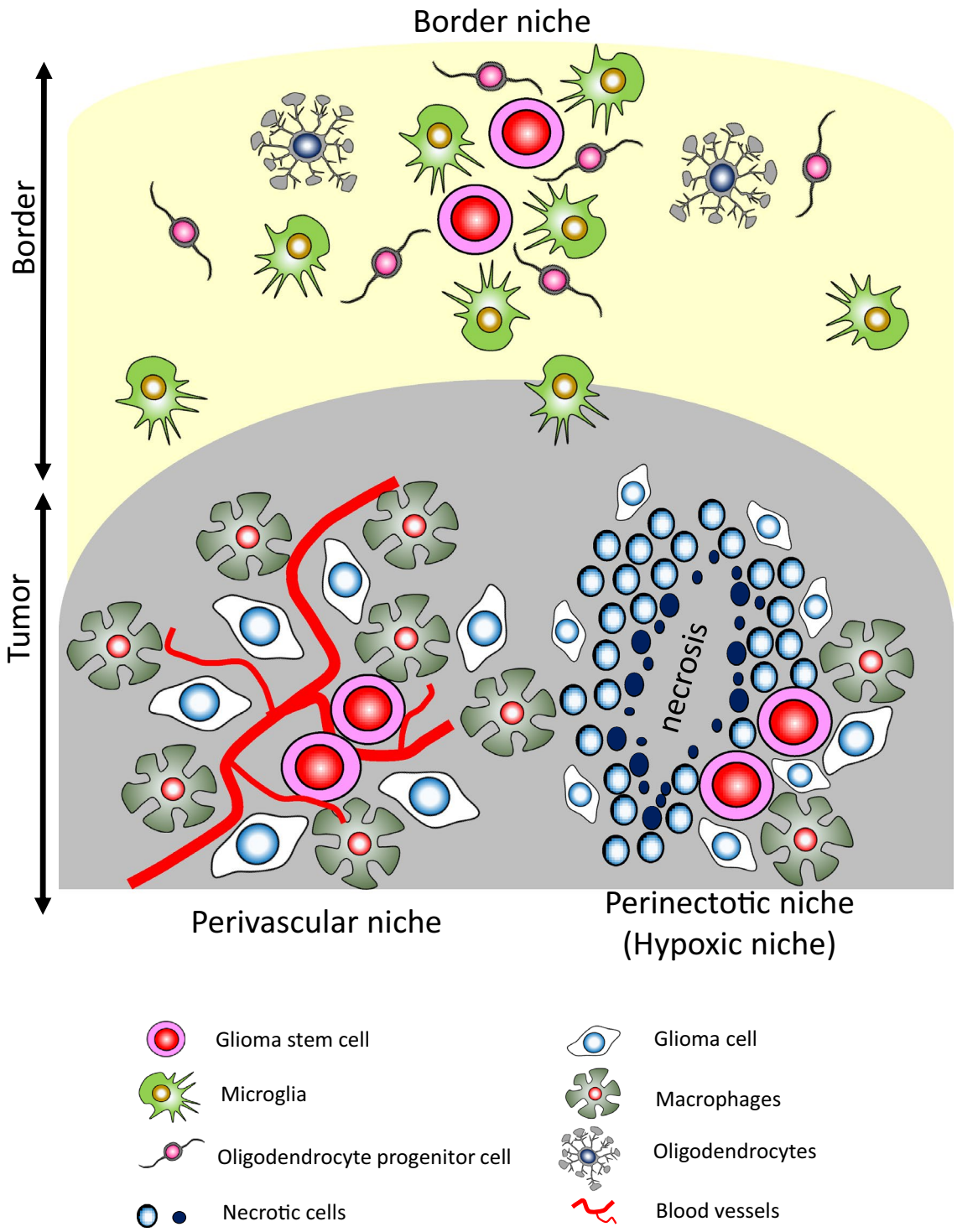


Fig. 4 Border niche, novel concept of special microenvironment in GBM. Previously, the perivascular niche and perinecrotic (hypoxic) niche have been described. Recent reports indicated that macrophages were mainly found at the perivascular area in the tumor. On the other hand, microglia accumulated at the edge of tumor. In the border area, OPCs and microglia accumulate and proliferate. GBM cells used these cells to form border niche for survival. OLCs exist abundantly in the tumor border but are rare within the tumor

migrate rapidly to sites of injury [49], and are known to occupy regions of traumatic brain injury within 1 day [50]. Their migration and proliferation speed is faster than that of astrocytes [51]. Neuronal activity also remodels white matter rapidly; for example, exercise stimulates OPC proliferation and oligodendrocyte production within only a few

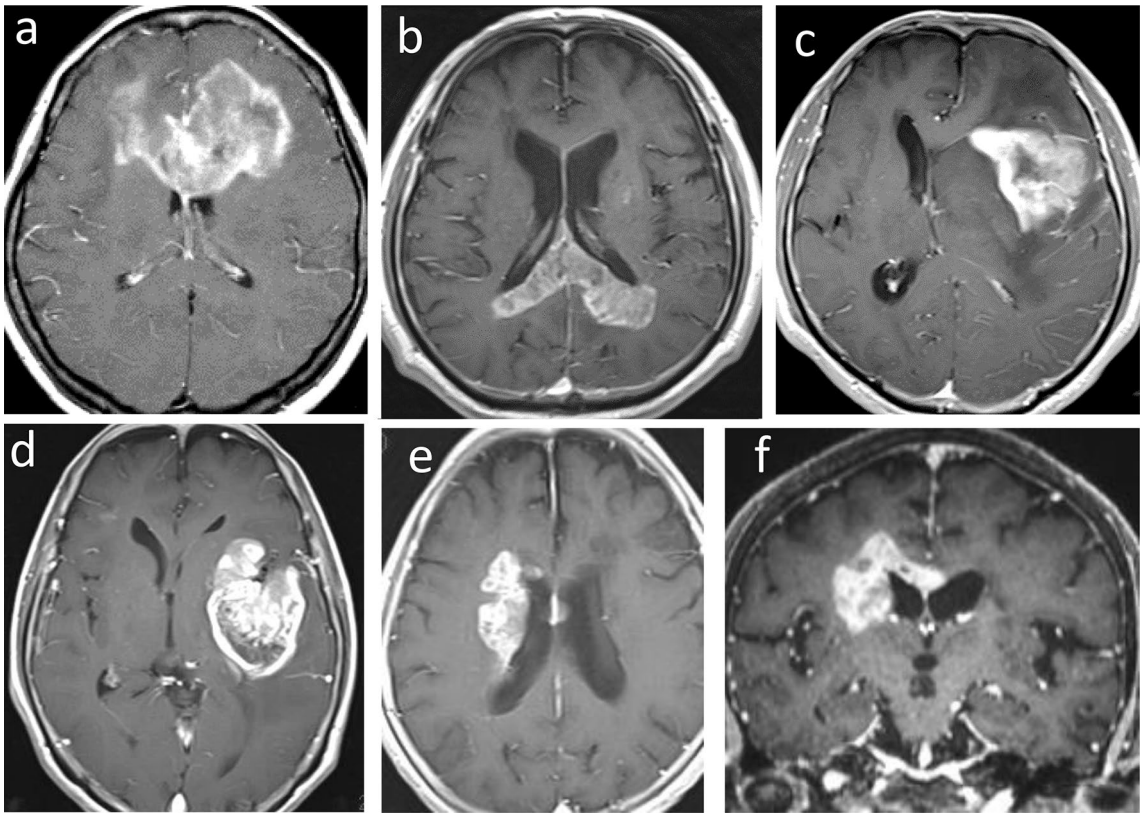


Fig. 5 Characteristic expansion pattern of GBM is related to fasciculus of myelinated axons. GBM cells preferentially migrate along the fasciculus of axons. **a**, **b** GBM cells migrate into the corpus callosum in commissural fibers, and form tumor masses in the bilateral hemispheres. **c** GBM expands along the radiation of the corpus callosum, **d** arcuate fasciculus in associated fibers. **e**, **f** GBM develops through the superior occipitofrontal fasciculus and superior longitudinal fasciculus in associated fibers and corpus callosum

days [52]. Thus, OPCs have been discussed in terms of their proliferation and re-myelination potential under non-tumoral conditions.

With regard to functional differences between OPCs in different sites, OPCs in forebrain white matter (corpus callosum) have a shorter cell division cycle (~ 10 days), than those in gray matter (motor cortex; ~ 36 days) of the mouse brain at 60 days after birth [53]. Interestingly, OLCs have been classified into 13 populations showing region- and age-specific distributions according to data from single-cell RNA sequencing of 5072 cells [54].

Further investigations are needed to describe functional variations between OLCs in the development and recurrence of GBM.

Other supportive cells in GBM microenvironments

Several types of 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 [13, 14, 39, 40, 55]. However, the microenvironments in which they formed were mainly in the tumor, not in the border area. The main cells populations in brain parenchyma are microglia, astrocytes, neurons, and OLCs. We, therefore, discuss candidate cells in present in the border niche below.

Microglia

Microglia-derived factors can influence oligodendrocyte lineage cells in terms of attraction, proliferation, differentiation, and myelination/re-myelination. Moreover, microglia enhance the differentiation of neural stem/progenitor cells into OLCs [56–58]. Under normal conditions, microglia migrate and proliferate in the brain, but in some insult conditions, macrophages invade the brain parenchyma through the impaired blood–brain barrier.

Recently, it was reported that bone-marrow-derived macrophages and resident microglia react differently to various types of CNS impairments. In GBM tissues, approximately 85% of glioma-associated macrophages/microglia (GAMs) infiltrate bone-marrow-derived monocyte/macrophages,

where resident microglia account for approximately remaining 15% [59]. Interestingly, bone-marrow-derived macrophages are prominent in perivascular areas, whereas resident microglia are present in high numbers in the peritumoral region [59, 60].

Because border niche exists in the peritumoral region, where abnormal vessels have not developed enough yet, majority of GAMs in the border niche are seemed to be microglia. Further investigations of microglia are needed to reveal fine mechanisms of border niche (Fig. 4).

Astrocytes

Astrocytes in the tumor microenvironment promote the proliferation, migration, and resistance to therapies of GBM cells [61, 62]. Interestingly, glioma-associated astrocytes (TAAs) have a different mRNA expression profile to normal astrocytes [63]. Astrocytes surrounding glioma biopsies secrete CCL2, which recruit macrophages and T cells. The majority of these accumulating T cells are regulatory T cells, which attenuate immune responses [64]. In addition, astrocytes appear to play indirect roles in the formation of the border niche, as they affect the proliferation and re-myelination of OPCs [65, 66]. However, astrocytes have a low proliferation rate and low migration potential to sites of wound injury [67]. Compared to astrocytes, OPCs and microglia play an immediate role in central nervous system injury [51]. These data suggest that OPCs and microglia play a more critical role in border niche formation than do astrocytes.

Neurons

Neuronal activities have a mitogenic effect on OPCs, and promote oligodendrogenesis, and increase myelination within the deep layer of the premotor cortex and subcortical white matter in mice [68]. Mitew et al. have presented fine data, showing that non-invasive pharmacogenetic stimulation of neuronal activity increases the proliferation and differentiation of OPCs in the corpus callosum, whereas attenuation of neuronal activity reduces myelination [69]. Thus, neuronal activity directly affects the migration and proliferation of OPCs.

One exiting possibility is that neuronal activity directly promotes the survival of GBM cells [70, 71]. Neural regulation of gliomas is dependent on the cleavage and secretion of the synaptic adhesion molecules neuroligin-3 (NLGN3), which promotes glioma proliferation through the PI3 K-mTOR pathway [70, 71]. This data suggests that molecules from neuron itself and also from proliferating OPCs regulated by neuronal activity promote survival and recurrence of GBM (Fig. 6a).

Circulating glioma cells form new lesions

Recently, the existence of circulating tumor cells (CTCs) in several types of cancers has been a topic of focus [72, 73]. In 2014, Muller reported that CTCs were identified in peripheral blood from 29 of 141 (20.6%) of GBM patients [74]. CTCs were detectable in 8 of 11 (72%) pre-radiotherapy patients, compared with 1 of 8 (13%) postradiotherapy patients [75]. In a transgenic mouse model, CTCs were found to exhibit stem cell-like properties, and to possess highly tumorigenic capacity. In GBM recurrence, CTCs may play an unexpected role as a CSC reservoir. CTCs colonized in the region of the primary tumor site to form new tumors. Interestingly, CTCs were localized in the border area of the primary tumor, contributing to local micro-metastasis and GBM heterogeneity [76]. Although the anatomical structure of tumor vessels is one of the factors of CTC settlement, the border niche formed with OPCs and microglia is crucial for settlement and recurrence (Fig. 4).

Border niches in recurrence

Taken together, during tumor growth, OPCs and microglia migrate and proliferate rapidly in the border area, where they secrete growth factors and cytokines. GBM cells make non-glioma cells adapt to supportive cells for themselves to survive and recur.

Standard approaches to GBM treatment are maximal safe resection, inhibition of local recurrence, and prevention of distant recurrence and dissemination. Primarily, decreasing the number of GBM cells is essential. Next, to prevent local recurrence, elucidation of the border niches is crucial. Photodynamic therapy [77, 78], BCNU wafer (Gliadel) [79–81], and high-dose radiation [82, 83] are regarded as beneficial therapies. However, there remain the issues of resistant circulating cells in peripheral blood and floating cells in cerebral spinal fluid (CSF) in patients with GBM. Several chemotherapeutic agents introduced by intravenous and intrathecal injection can attack these cells. To prevent recurrence, the application of not only local intensification therapies, but also therapies targeting CTCs in blood and floating cells in CSF should be applied just after surgical operation, before remodeling of the border niche [8].

From several lines of evidences, GBM cells have affinity for, and migrate into, the fasciculus of myelinated axon fibers, where OLCs and OPCs exist abundantly. OPCs respond to stimuli from neurons, microglia, and GBM cells (Fig. 6a). To prevent local recurrence, further

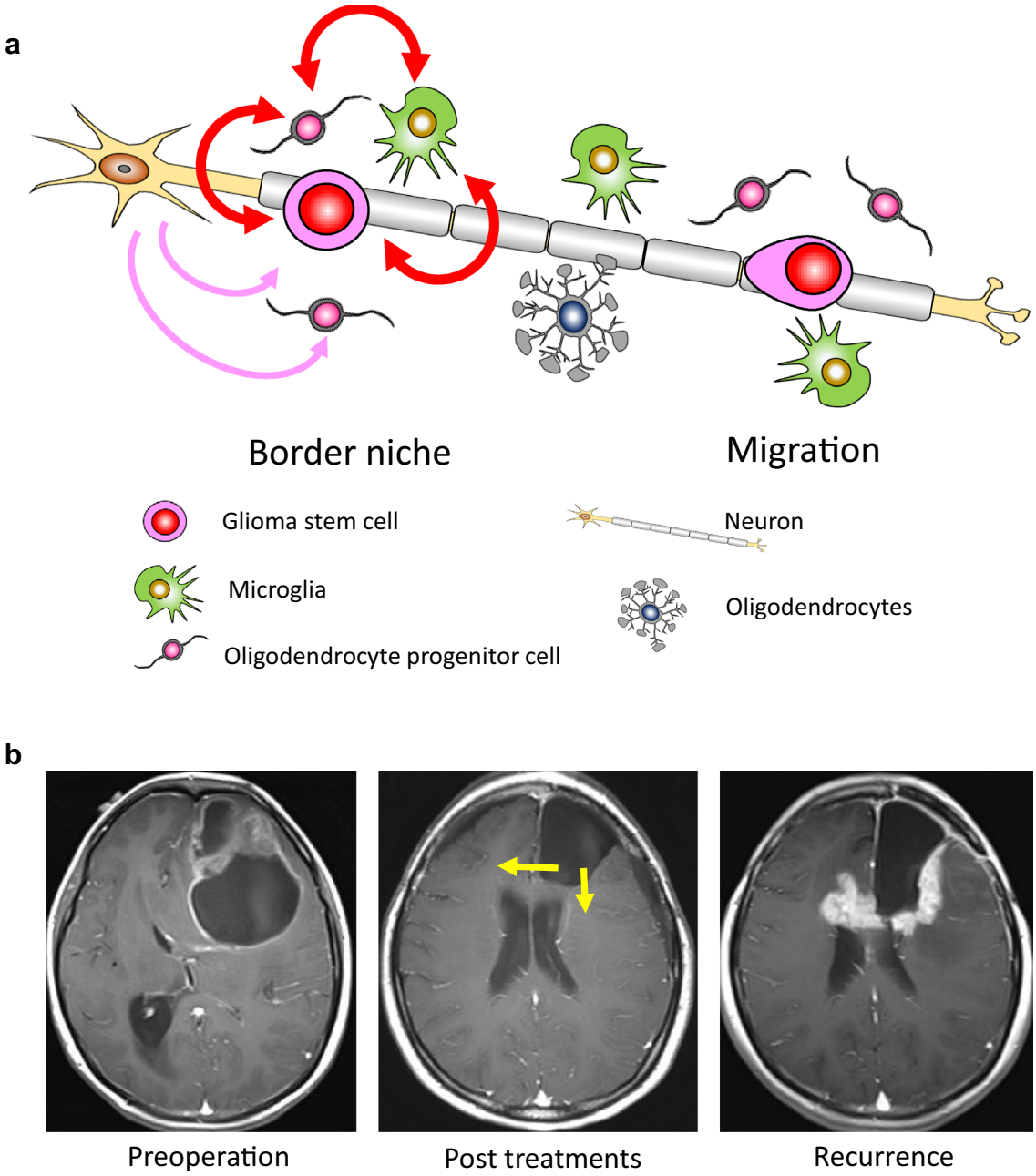


Fig. 6 Proliferation, recurrence, and migration of GBM in border niche. **a** Crosstalk between GBM cells and non-GBM cells, OPC and microglia, promotes stemness and therapeutic resistance in GBM cells in the border niche (red arrow). Neuronal activity induces proliferation of not only OPCs, but also of GBM cells (pink arrow). GBM cells prefer to migrate within the fasciculus of axons, where abundant OLCs and OPCs exist. The border niche is characterized by glioma-associated oligodendrocytes (GAOs) and microglia. **b** GBM recurrence is predicted along the fasciculus of axons (yellow allow). Prediction of areas of recurrence and precautionary focal therapies on these areas might improve survival and quality of life for patients with GBM

accumulating image analysis can be applied to predict the sites of remaining border niches and the direction of GBM expansion (Fig. 6b). Suppression of local recurrence and restriction of invasion into adjacent eloquent areas by preventative focal therapies can improve overall survival and quality of life in patients with GBM. Thus, studies of tissue external to the main tumor mass are a fundamental strategy that can lead to simple and universal solutions capable of effectively treating lethal GBM tumors.

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