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Review

Dynamics of bone marrow-derived cells relevant to the brain-immune cell-cell interactions under non-inflammatory conditions

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ABSTRACT

Although recent data indicates that the central nervous system is interactive with the peripheral immune system, the site of cell-cell interaction between brain cells and immune cells remains to be determined. Studies using bone marrow chimeras have consistently shown that bone marrow-derived cells under non-inflammatory conditions are located in the leptomeninges, choroid plexuses, perivascular spaces and circumventricular organs (CVOs), suggesting that these structures are the brain-immune interface. However, there has been some controversy over whether bone marrow-derived cells infiltrate the brain parenchyma, which is protected by the blood-brain barrier. Recently we investigated the distribution, density and differentiation of bone marrow-derived cells in the brain parenchyma in a non-inflammatory condition by intra-bone marrow-bone marrow transplantation (IBM-BMT). In addition to the meningeal space and CVOs, bone marrow-derived cells appear in certain specific brain parenchymal regions and exhibit multiple ramified processes with myeloid lineage differentiation. Most of these discrete regions are adjacent to the attachments of choroid plexus that comprise of thinned brain parenchyma consisting of astrocytic processes in the narrow channel between the ependyma and pia. These astrocytic processes express CX3CL1, a possible chemoattractant for myeloid lineage cells. In the choroid plexus stroma, there are clusters of myeloid cells, 80% of which are replaced by newly generated cells originating in the bone marrow during the 8-month period following IBM-BMT. Furthermore, CXCL12-expressing cells and ER-TR7-expressing cells are present in the choroid plexus stroma. Based on this collection of cells in the choroid plexus, we propose that the choroid plexus stroma may function as a niche for bone marrow-derived myeloid cells and as a mechanism for supplying them continuously to the brain parenchyma via the attachments of choroid plexus. We discuss that potential changes in the dynamics of bone marrow-derived myeloid cells and their interactions with brain cells may be involved in neurological and psychiatric disorders.

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KEYWORDS: bone marrow transplantation, choroid plexus, immune system, stromal cells, cytokine

INTRODUCTION

It has been widely assumed that the central nervous system (CNS) is an immune-privileged organ [1]. CNS immune privilege was experimentally defined by the fact that tissues rapidly rejected by the immune system when grafted in sites such as the skin, show prolonged survival when grafted into the CNS [2]. Isolation of the brain from the immune system by the blood-brain barrier (BBB) and the lack of draining lymphatics also contributed to the construction of brain immune privilege [3]. However, recent data have dramatically altered this viewpoint by revealing that the CNS is both immune competent and actively interactive with the peripheral immune system.

The immune system modulates the functional and behavioral processes of the CNS under inflammatory conditions [4]. Exposure to pathogens stimulates the peripheral immune system and induces inflammatory responses, including the elevated expression of pro-inflammatory cytokines such as interleukin (IL)-1 [5, 6], IL-6, and TNF-α [7]. Increased levels of pro-inflammatory cytokines in peripheral tissues induce the local synthesis of pro-inflammatory cytokines within the brain parenchyma [8-10], leading to behavioral alteration such as sickness behavior [11-13] and impaired learning [14]. The immune system also plays an important role in maintaining the higher functions of the brain under non-inflammatory conditions. For example, severe combined immune deficiency mice and nude mice that are deficient in mature T cells exhibit cognitive deficits and behavioral abnormalities that are remedied by T cell restoration [15]. In addition, systemic depletion of CD4-positive T cells leads to reduced hippocampal neurogenesis and impaired learning in the Morris water maze [16]. T cells are not normally present in the brain parenchyma under non-inflammatory conditions, but during cognitive task performance, it is necessary that T cells accumulate in the meninges and express high levels of IL-4, which skews meningeal myeloid cells toward an anti-inflammatory phenotype [17, 18].

Although the brain is now known to be actively interactive with the immune system under non-inflammatory conditions, the site of cell-cell interaction between brain parenchymal cells and immune cells remains to be determined. Studies using bone marrow chimeras suggest that the leptomeninges, choroid plexuses, perivascular spaces and circumventricular organs (CVOs) are the potential brain-immune interface. In this review, we suggest that small discrete regions of the brain parenchyma that are consistently adjacent to the attachments of choroid plexus could be another brain-immune interface. Based on our histological analyses, we propose that the choroid plexus may function as a niche for bone marrow-derived cells and as a mechanism for supplying them to the brain in a non-inflammatory condition, and discuss the potential involvement of the altered dynamics of bone marrow-derived cells in neurological and psychiatric disorders.

1. Intra-bone marrow bone marrow transplantation as a tool to elucidate the potential sites for brain-immune cell-cell interactions

What is the site of cell-cell interaction between brain parenchymal cells and immune cells under non-inflammatory conditions? One of the most powerful tools for addressing this question is to create bone marrow chimera in which the recipients' immune system is reconstituted with a donor's labeled bone marrow cells (BMCs) by transplantation, since this allows us to trace the distribution of labeled immune cells entering any specific organ. Studies using bone marrow chimeras to examine the brain distribution of bone marrow-derived cells have been reported since the late 80s [19]. These studies have consistently shown that under non-inflammatory conditions bone marrow-derived cells are primarily located in the leptomeninges, choroid plexus and perivascular spaces [20-25]. Bone marrow-derived cells also enter the CVOs, which contain a high density of capillaries lacking BBB [21]. These bone marrow-derived cells have been reported to preserve hematopoietic identity or express markers of the myeloid lineage.

However, there has been some controversy over whether bone marrow-derived cells infiltrate the

brain parenchyma that is protected by the complete BBB, under non-inflammatory conditions. Some investigators have stated that, after bone marrow transplantation (BMT) by intravenous (IV) injection of donor cells, donor-derived cells were widely distributed throughout the brain parenchyma and differentiated into microglia with a highly ramified morphology [26, 27]. Others have claimed that the donors' bone marrow-derived cells were found chiefly in association with blood vessels, and only rarely in the parenchyma of the brain [20, 21, 23]. It is now known that postnatal hematopoietic progenitors do not significantly contribute to microglia renewal or homeostasis in the adult brain [28].

Meanwhile, a novel BMT procedure, namely intra-bone marrow (IBM)-BMT has been developed. In this procedure, BMCs are collected from the marrow of the donors' long bones by perfusion, and whole BMCs are injected directly into the bone marrow cavity of the recipients instead of being injected IV [29, 30]. The IBM procedure facilitates the efficacious and speedy transfer of not only hematopoietic stem cells (HSCs) but also mesenchymal stem cells (MSCs) from donor into recipient [31]. HSCs grow and survive in conjunction with major histocompatibility complex-compatible mesenchymal cells [32]. During the early period (2-6 days) after BMT, there are higher numbers of both HSCs and MSCs in the bone marrow cavity in chimeras prepared by the IBM procedure than those by the IV procedure [33]. In particular, the number of donor-derived MSCs in the bone marrow 6 days after IBM-BMT is about ten times that after IV-BMT [33]. The chemotactic factors that can promote the migration of MSCs are produced by the bone marrow collected from irradiated mice 4 hours after irradiation, which lasts for at least 4 days. In contrast, the sera collected from irradiated mice at the same timing exhibit no chemotactic activity, indicating that IV-administered MSCs cannot effectively home to the recipients' bone marrow cavity [33]. One of the striking advantages of IBM-BMT is that, when IBM-BMT is performed at the same time as the transplantation of heterotopic organs, it facilitates the induction of persistent donor-specific tolerance without rejection and reduces the incidence of graft versus host disease to far below the incidence level when the IV-BMT method is used [34-38].

2. Leptomeninges, perivascular spaces, choroid plexuses and circumventricular organs as the brain-immune interface

We investigated the distribution and time-dependent changes in the density of bone marrow-derived cells as well as their differentiation in the brain in a non-inflammatory condition, in bone marrow chimeric mice produced by the IBM procedure [39]. Bone marrow-derived cells appear in the leptomeninges and choroid plexus stroma 2 weeks after BMT and in the brain perivascular spaces 1 month after BMT in the chimera (Figure 1). In the leptomeninges, the bone marrow-derived cells are round or spindle-shaped. The spindle-shaped bone marrow-derived cells are found along the blood vessel walls and along the pia, and in the latter case, they are in close apposition to subpial astrocytic endfeet (Figure 2A). Since the perivascular space is a narrow space between the outer surface of capillary walls and the surface of brain parenchyma, bone marrow-derived cells that have entered the perivascular space are in close apposition to perivascular astrocytic endfeet (Figure 2B). In the choroid plexus stroma, bone marrow-derived cells with a round to ovoid morphology are often found in clusters (Figure 2C). Isolated, scattered bone marrow-derived cells exhibit a spindle-shaped morphology without ramified processes. Leptomeninges, perivascular spaces and choroid plexus stroma share tissue components that are contiguous (meningeal space), as will be discussed in section 5. Therefore, meningeal space is one of the interfaces between the immune system and the brain.

The distribution of the bone marrow-derived cells in the meningeal space is reasonable because our ongoing study suggests that cells constructing the meningeal space play an important role in transmitting pathogen-stimulated peripheral immune activation to the brain parenchyma. Multiplex cytokine assays of brain homogenates prepared from mice 1-24 hours after i.p. injection of lipopolysaccharide (LPS) highlighted ten cytokines that increased in concentration in the hippocampus after LPS injection (unpublished data). The concentrations of these cytokines returned to the basal levels 48 hours after LPS injection, indicative of a homeostatic regulation of the cytokine microenvironment of the brain parenchyma.

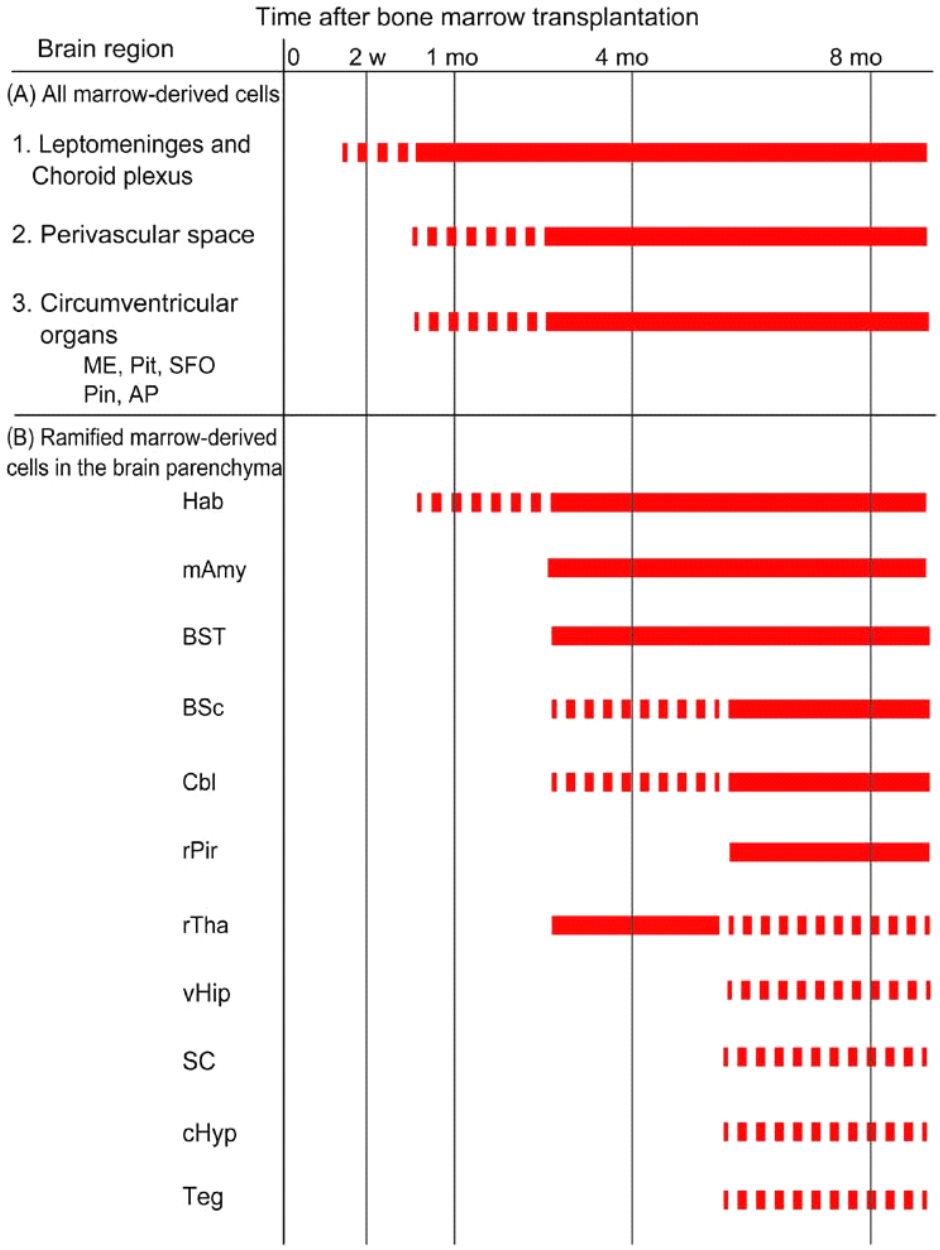

Figure 1. Chronological patterns of the entry of marrow-derived cells into the meningeal space and the brain parenchyma following bone marrow transplantation by IBM-BMT. (A) The presence of all bone marrow-derived cells without regard to morphology was examined in the leptomeninges, choroid plexus, perivascular space and circumventricular organs such as ME, median eminence; Pit, posterior pituitary; SFO, subfornical organ; Pin, pineal gland; and AP, area postrema. Solid lines indicate the definitive presence of marrow-derived cells. Dotted lines indicate the presence of marrow-derived cells at relatively low density. **(B)** Bone marrow-derived cells with ramified morphology were counted quantitatively in Hab, habenula; mAmy, medial amygdala; BST, bed nucleus of stria terminalis; BSc, brain stem cochlear nucleus; Cbl, cerebellar cortex; rPir, rostral piriform cortex; rTha, rostral thalamus; vHip, ventral hippocampus; SC, superior colliculus; cHyp, caudal hypothalamus; and Teg, tegmentum. Solid lines indicate the presence of marrow-derived cells with ramified morphology at a density of 4 cells/mm^2 or more. Dotted lines indicate the presence of marrow-derived cells with ramified morphology at a density of 2 cells/mm^2 or more and less than 4 cells/mm^2. Modification of copyrighted material permitted by Academic Press [39], License Id: 3542250358165.

Cells of the meningeal space were the major sources of most of these cytokines that were elevated in the hippocampus 4 hours after LPS injection or earlier. Receptors for these cytokines were expressed on perivascular astrocytic endfeet. Some cytokines were elevated in astrocytic cell bodies in the hippocampus 24 hours after LPS injection. These results suggest that cells located in the brain-immune interface are involved in the mechanism underlying the homeostasis of the brain cytokine microenvironment.

Since the CVOs lack the BBB, bone marrow-derived cells readily enter the median eminence, posterior pituitary, subfornical organ, pineal gland and area postrema 1 month after BMT. Most bone marrow-derived cells in the CVOs are closely associated with blood vessels, and exhibit elongated cell bodies with rare ramified processes. Therefore, CVOs constitute another interface between the immune system and the brain.

3. Distribution and differentiation of bone marrow-derived cells in the brain parenchyma

Some particular regions of the brain parenchyma are populated by clusters of bone marrow-derived cells [39]. These regions are relatively small in size and discrete. Bone marrow-derived cells in these particular regions frequently exhibit multiple ramified processes (ramified marrow-derived cells). All ramified marrow-derived cells express Iba-1, a myeloid cell marker. No ramified marrow-derived cells express S-100β, an astrocyte marker, CNPase, an oligodendrocyte marker or NeuN, a neuron marker.

In chimeric mice receiving the IBM procedure, most of the ramified marrow-derived cells start to appear 4 months after BMT, although the earliest cells appear 1 month after BMT in restricted areas such as the habenula [39]. The density of ramified marrow-derived cells further increases thereafter, as a function of post-BMT time up to 8 months. Ramified marrow-derived cells are distributed with the highest density (> 16 cells/mm^2) in the habenula and the brain stem cochlear nucleus, followed by the medial amygdala and the bed nucleus of stria terminalis (8-16 cells/mm^2). They are distributed with moderate densities (4-8 cells/mm^2) in the piriform cortex, thalamus and cerebellar cortex. In the ventral hippocampus, superior colliculus, hypothalamus and midbrain tegmentum, ramified marrow-derived cells are distributed at relatively low densities (2-4 cells/mm^2).

4. The attachments of choroid plexus, a potential bridging channel via which bone marrow-derived cells travel to the brain parenchyma

Most of the regions where ramified marrow-derived cells are located contain junctions at which the choroid plexuses of the ventricles are attached to the brain parenchyma. In the lateral ventricle, the choroid plexus is formed by the papillary protrusion of leptomeninges toward the inside of the ventricular cavity, where they bridge the stria terminalis and medial amygdala. The choroid plexus stroma shares tissue components with the leptomeninges and consists of loose connective tissue containing many capillaries. The choroid plexus epithelial cells are a continuation of the ependymal cells. At the edge of the stria terminalis or medial amygdala, the brain parenchyma is extremely thinned and consists of loose wavy fibrous processes of astrocytes that are located in the narrow channel between the ependyma and pia (Figure 3). We call this particular structure, which consists of ependyma, loose glial tissue and pia that connect the brain parenchyma and the choroid plexus, the ‘attachments of choroid plexus’.

In the choroid plexus stroma, bone marrow-derived cells exhibit a round to ovoid morphology. When bone marrow-derived cells are located inside the attachments of choroid plexus, they are spindle-shaped and often exhibit a tortuous appearance with sharp bends. Once these cells enter the brain parenchyma, they cluster in a relatively small area and differentiate into a ramified morphology (Figure 4). This transition of morphology raises the possibility that marrow-derived cells enter the brain parenchyma through the attachments of choroid plexus, suggesting that there is some specific molecular basis for the enhancement of such emigration of bone marrow-derived cells.

One of the candidate molecular cues is the CX3CL1-CX3CR1 signaling system. CX3CL1 (or fractalkine) is strongly expressed in the attachments of choroid plexus in both BM-transplanted and

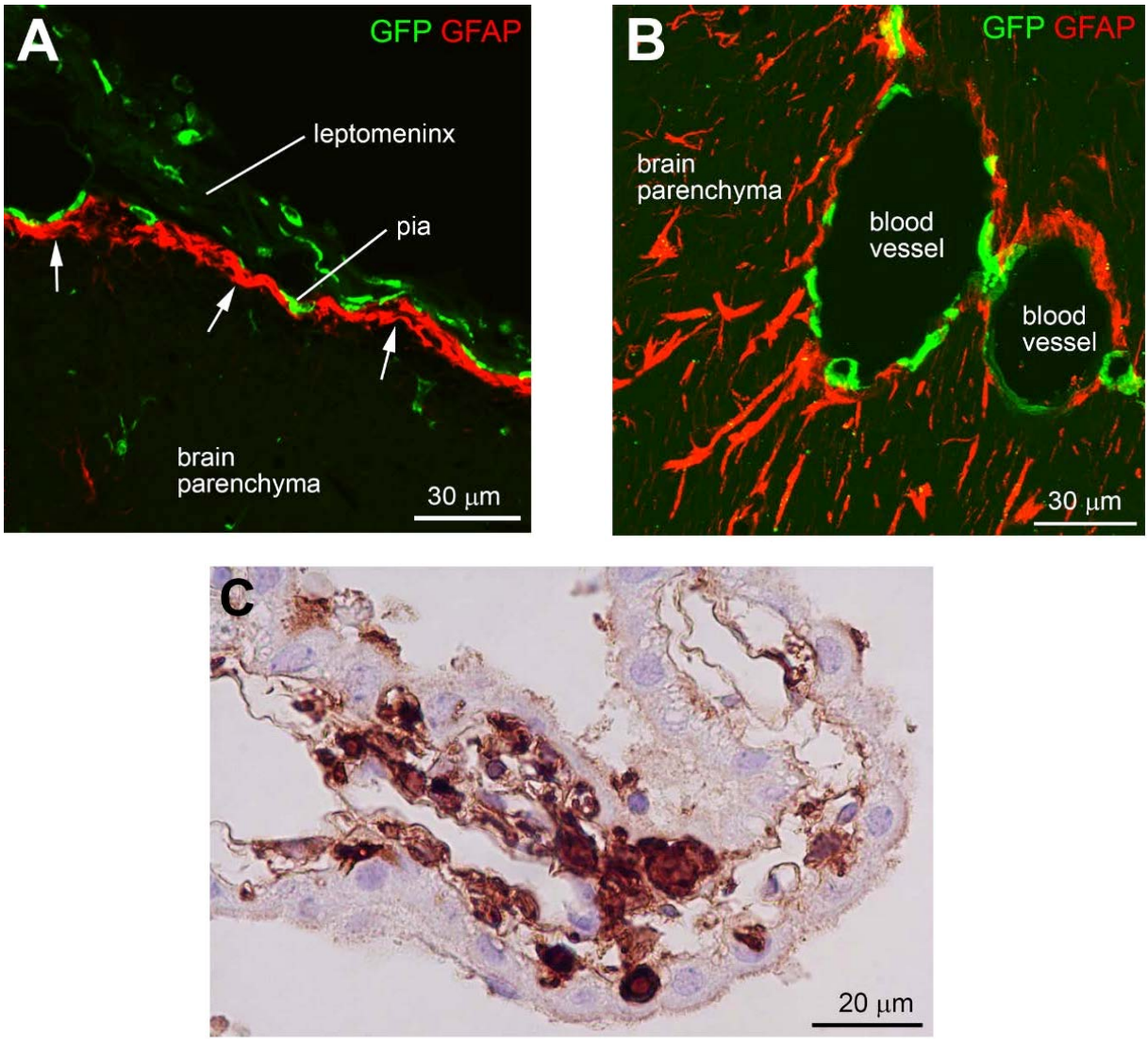

Figure 2

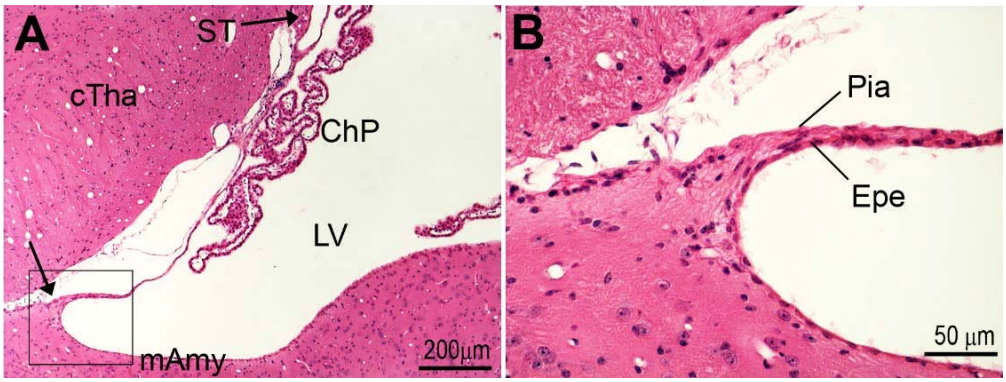

Figure 3

non-treated mice in a similar manner. CX3CL1 is constitutively expressed in particular portions of fibrous cytoplasmic processes emanating from astrocytes whose cell bodies are located in the adjacent brain parenchyma. It is known that monocyte-derived cells in the choroid plexus and microglia in the brain parenchyma express CX3CR1 [24], a highly specific receptor for CX3CL1 [40]. CX3CL1 is a transmembrane molecule with a unique CX3C-motif whose expression is induced by inflammatory cytokines [41]. It functions as a cell adhesion molecule for CX3CR1-expressing cells including monocytes [40]. Membrane-anchored CX3CL1 can be released from the cell surface by the cleavage and shedding mediated by ADAM (A Disintegrin And Metalloproteinase)10 and ADAM17 [42, 43]. Soluble CX3CL1 functions as a chemoattractant for cells bearing CX3CR1 [40, 41]. The CX3CL1-CX3CR1 signaling system is required for physiological trafficking of circulating monocytes to organs such as lung [44] and small intestine [45]. Therefore, it is possible for bone marrow-derived cells lining up along the narrow channel of the attachments of choroid plexus to make cell-to-cell contact with CX3CL1-expressing astrocytic processes, resulting in trafficking into the brain parenchyma (Figure 5).

5. Colonization of choroid plexus stroma by bone marrow-derived cells relevant to the brain-immune interactions

There are clusters of bone marrow-derived cells with the myeloid lineage in the choroid plexus stroma, as evidenced by studies using chimera. During the period of 8 months following IBM-BMT, more than 80% of myeloid lineage cells in the choroid plexus stroma are replaced by newly generated cells originating in the bone marrow. This intensive colonization of choroid plexus stroma by bone marrow-derived myeloid cells suggests that the choroid plexus stroma serves as a niche for myeloid progenitors. Based on *in vitro* experiments, the choroid plexus stroma has been reported to construct a niche for myeloid progenitors [46].

The importance of stromal tissues in the lymphoid organs has recently been revisited. The proper function of the immune system is dependent on interactions between hematopoietic cells and non-hematopoietic stromal cells that form the micro-environments in which immune responses occur [47]. This collection of cells is also referred to as the immune stroma. It creates a microenvironment in which the immune system operates, providing an architectural landscape for hematopoietic cell-cell interactions and molecular cues governing hematopoietic cell positioning, growth, and survival [48]. It is the organization of stromal cell networks that constitutes the HSC niche in the primary lymphoid organs and the microenvironment in the secondary lymphoid organs (SLOs). Recent studies have revealed the molecular and cellular components of the HSC niche in the bone marrow. The molecular components include stem cell factor, CXCL12, angiopoietin-1, and thrombopoietin, etc., and the cellular components include perivascular

Legend to Figure 2. Leptomeninges, perivascular spaces and choroid plexuses as the brain-immune interface. (A and B) Double immunofluorescence staining for GFP and Glial fibrillary acidic protein (GFAP) of chimeric mice produced by the IBM-BMT reveals that bone marrow-derived cells are round or spindle-shaped in the leptomeninges **(A)**. Some spindle-shaped bone marrow-derived cells are found along the pia and in close apposition to subpial astrocytic endfeet (A, arrows). **(B)** Bone marrow-derived cells located in the perivascular space are in close apposition to perivascular astrocytic endfeet. **(C)** Immunohistochemical staining for GFP reveals that bone marrow-derived cells with a round to ovoid morphology are often found in clusters in the choroid plexus stroma. (C) is a modification of copyrighted material permitted by Academic Press [39] with License Id: 3542250358165.

Legend to Figure 3. The attachments of choroid plexus. (A) Hematoxylin and eosin (H&E)-stained sections indicate that the choroid plexus (ChP) of mice is developed as a papillary protrusion into the lateral ventricle (LV) and derived from the leptomeninges connecting the edges of the stria terminalis (ST) and medial amygdala (mAmy) like a bridge. Arrows indicate both edges. cTha, caudal thalamus. **(B)** A magnified view of the inset in A indicates that the attachments of choroid plexus consist of extremely thinned brain parenchyma formed with loose fibrous tissue located in a narrow channel between the pia (Pia) and ependyma (Epe). Reproduction of copyrighted material permitted by Academic Press [39], License Id: 3542250358165.

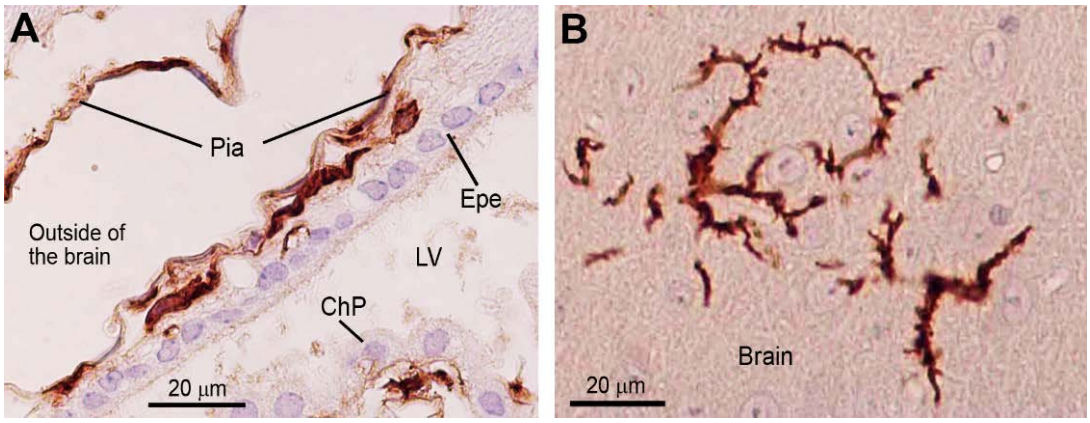

Figure 4

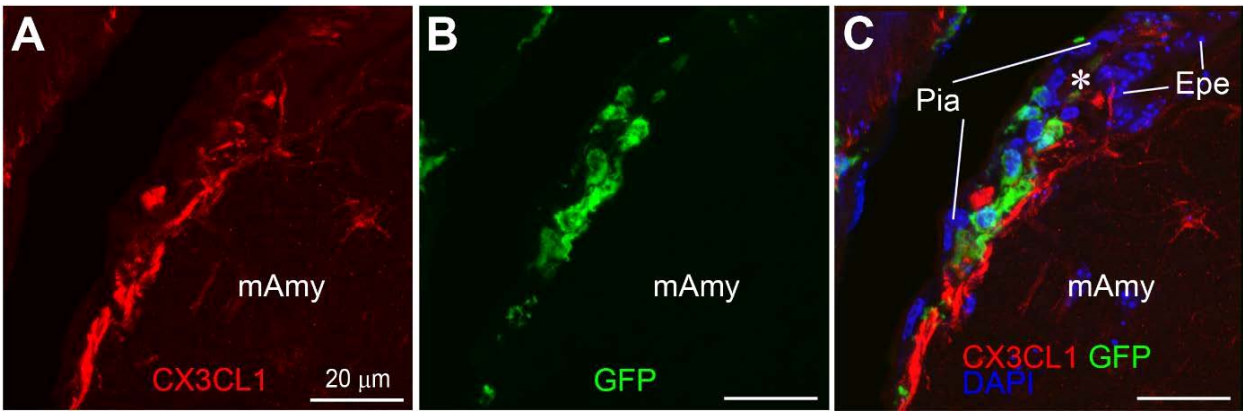

Figure 5

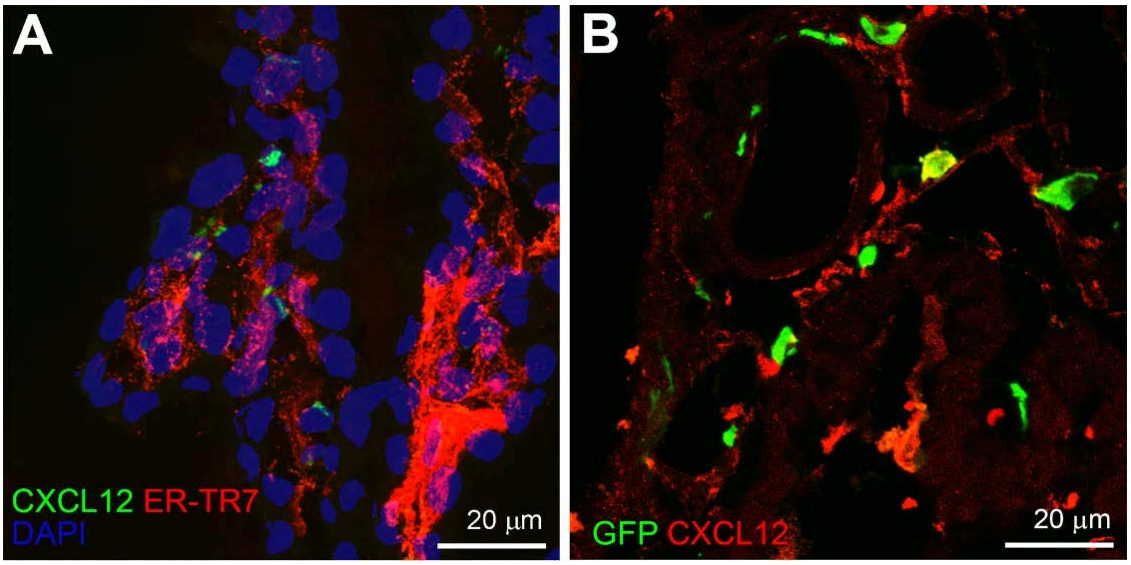

Figure 6

mesenchymal stem cells, CXCL12-abundant reticular (CAR) cells, endothelial cells, osteoprogenitors, and bone marrow fibroblasts, etc. [49-54]. The stromal cell subsets that make up the parenchyma of SLOs include fibroblastic reticular cells (FRCs), follicular dendritic cells (FDCs), marginal reticular cells (MRCs), splenic red pulp fibroblasts and lymph node medullary fibroblasts, in addition to the vascular and lymphatic endothelial cells [48, 55]. FRCs in SLOs produce collagen-rich reticular fibers and surround the central arterioles and venules, forming a dense meshwork filled with lymphocytes [56]. Lymphocytes in the meshwork are in constant dynamic motion and move along FRC strands that act as guidance paths for cell migration [57].

Since FRCs in SLOs are known to express extracellular matrix components such as ER-TR7 [55], we are examining the choroid plexus stroma immunohistologically using anti-ER-TR7 antibody. The results suggest the presence of cells reminiscent of FRCs in the choroid plexus stroma (Figure 6A). Our previous studies have shown the presence of some CXCL12-expressing cells scattered throughout the choroid plexus stroma that exhibit multiple radiating elongated thin cytoplasmic processes similar to CAR cells of the bone marrow stroma [39]. The CXCL12-expressing cells are in close apposition to bone marrow-derived cells in the choroid plexus stroma. Interestingly, some of these CXCL12-expressing cells are derived from bone marrow (Figure 6B).

CX3CL1 mRNA transcripts are detectable by Reverse Transcription Polymerase Chain Reaction (RT-PCR) in the brain tissue consisting of the choroid plexus, the attachments of choroid plexus and adjacent small brain parenchyma. Transcripts of CX3CR1, ADAM10, CXCL12 and CXCR4, a receptor for CXCL12, are also detectable by RT-PCR in the same brain regions [39]. These results suggest that the choroid plexus stroma may function as a niche for bone marrow-derived myeloid cells and as a mechanism for supplying myeloid cells continuously to the brain parenchyma via the attachments of choroid plexus, although further studies to confirm this notion are necessary.

6. Relevance to neurological and psychiatric diseases

Bone marrow-derived cells that enter the brain parenchyma increase in number in animal models for ischemic brain injury [22, 58, 59] and status epilepticus [60, 61], as well as in animal models of neurodegenerative diseases such as Alzheimer's disease [62], Parkinson's disease [63, 64] and amyotrophic lateral sclerosis [65, 66]. In experimental

Legend to Figure 4. Morphological ramified marrow-derived cells in the brain parenchyma expressing a myeloid lineage marker. Immunohistochemical staining for GFP of chimeric mice produced by the IBM-BMT reveals that marrow-derived cells located in the space between the pia (Pia) and ependyma (Epe) exhibit spindle-shaped, tortuous appearance with sharp bends without ramified processes **(A)**. Once these cells enter the brain parenchyma such as the medial amygdala, they cluster in a relatively small area and differentiate into ramified morphology **(B)**. Nuclei were counterstained with hematoxylin. ChP, choroid plexus; LV, lateral ventricle. Modification of copyrighted material permitted by Academic Press [39], License Id: 3542250358165.

Legend to Figure 5. Bone marrow-derived cells in close apposition to CX3CL1-expressing astrocytic processes of the attachments of choroid plexus. Double immunofluorescence staining for GFP (green) and CX3CL1 (red) indicates the lining up of GFP-immunopositive bone marrow-derived cells along the narrow channel (asterisk) formed between the pia (Pia) and ependyma (Epe) in the attachments of choroid plexus on the medial amygdala (mAmy). This location suggests a cell-to-cell contact between bone marrow-derived cells and CX3CL1-immunopositive astrocytic processes in chimeric mice after IBM-BMT. Modification of copyrighted material permitted by Academic Press [39], License Id: 3542250358165.

Legend to Figure 6. Cellular component of the choroid plexus stromal tissue. (A) Double immunofluorescence staining for CXCL12 (green) and ER-TR7 (red) indicates the presence of reticular fibers forming a dense meshwork reminiscent of fibroblastic reticular cells (FRCs) in the choroid plexus stroma. There are also some scattered CXCL12-expressing cells in the choroid plexus stroma. **(B)** Double immunofluorescence staining for GFP (green) and CXCL12 (red) indicates that the CXCL12-expressing cells are in close apposition to bone marrow-derived cells in the choroid plexus stroma. Some of the CXCL12-expressing cells are derived from bone marrow.

allergic encephalomyelitis, the choroid plexus is known as the CNS lymphocyte entry point [67]. In a stroke model, bone marrow-derived perivascular, meningeal and choroid plexus macrophages play an integral role in the inflammatory cascade [68].

Neuroinflammatory status, cytokine imbalance or altered immune-brain interactions are involved in a wide variety of neurological and psychiatric disorders such as neonatal periventricular leukomalacia [69-71], autism spectrum disorders [72], schizophrenia [73], depression [74], and aging and dementia [75-78]. Repeated social defeat [79] and LPS-induced peripheral immune activation increase the recruitment of bone marrow-derived cells into the brain [80].

Age-related neurodegenerative conditions may be associated with altered recruitment of bone marrow-derived cells into the brain. The senescence-accelerated mouse prone 10 (SAMP10) is an animal model of human brain aging and undergoes early onset neurodegeneration compared to normal strains of mice, including C57BL/6 (B6) [81-91]. We hypothesized that the dynamics of immune cells migrating from the bone marrow to the brain is perturbed in SAMP10 mice. In our recent project, we created 4 groups of bone marrow chimeras by IBM-BMT using 2- and 10-month-old SAMP10 and B6 mice as recipients with Green Fluorescent Protein (GFP) transgenic B6 mice at the age of 5 weeks as donors, and histologically analyzed them 4 months later. In the (B6 → 10 month-old SAMP10) chimeras, more ramified marrow-derived cells populated a larger number of discrete brain regions than the other chimeras, especially in the diencephalon [92]. Thus, the brain-immune interaction was perturbed in the SAMP10 mice. The diencephalic structures located along the midline at the dorsal and ventral edges such as the choroid plexus epithelium, ependyma, astrocytic processes in the attachments of choroid plexus, periventricular astrocytes, tanycytes, median eminence and hypothalamic neurons elevated the tissue concentrations of CXCL1, CCL11, G-CSF and CXCL10. Changes in the cytokine profile are very likely to contribute to acceleration of the dynamics of immune cells migrating from the bone marrow to the diencephalon. These studies and our future experiments will enhance our understanding of the cytokine-based mechanism underlying the homeostatic regulation of cell-cell interactions between the brain and bone marrow. In addition, further studies should address the functional roles of ramified marrow-derived myeloid cells in the brain.

CONCLUSIONS

Bone marrow-derived cells with the myeloid lineage enter certain specific brain parenchyma in non-inflammatory conditions from the choroid plexus stroma through the attachments of choroid plexus that comprise of astrocytic processes in the narrow channel between the ependyma and pia. CX3CL1 expressed by the astrocytic processes is a possible chemoattractant for myeloid cells. Once marrow-derived myeloid cells enter the brain parenchyma, they differentiate into ramified cells. The choroid plexus stroma contains CXCL12-expressing cells and ER-TR7-expressing reticular cells in addition to myeloid cells. The choroid plexus stroma may function as a niche for marrow-derived myeloid cells and as a mechanism for supplying them continuously to the brain parenchyma via the attachments of choroid plexus. In a mouse model of neurodegeneration, changes in the brain cytokine profile contribute to acceleration of the dynamics of immune cells migrating from the bone marrow to the brain. Further investigations addressing the cytokine-based mechanism underlying the homeostatic regulation of the brain-immune cell-cell interactions as well as the functional roles of ramified marrow-derived myeloid cells in the brain are warranted.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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