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Brain perivascular macrophages: characterization and functional roles in health and disease

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Abstract

Perivascular macrophages (PVM) are a distinct population of resident brain macrophages characterized by a close association with the cerebral vasculature. PVM migrate from the yolk sac into the brain early in development and, like microglia, are likely to be a self-renewing cell population that, in the normal state, is not replenished by circulating monocytes. Increasing evidence implicates PVM in several disease processes, ranging from brain infections and immune activation to regulation of the hypothalamic-adrenal axis and neurovascular-neurocognitive dysfunction in the setting of hypertension, Alzheimer disease pathology, or obesity. These effects involve crosstalk between PVM and cerebral endothelial cells, interaction with circulating immune cells, and/or production of reactive oxygen species. Overall, the available evidence supports the idea that PVM are a key component of the brain-resident immune system with broad implications for the pathogenesis of major brain diseases. A better understanding of the biology and pathobiology of PVM may lead to new insights and therapeutic strategies for a wide variety of brain diseases.

Keywords

Brain perivascular macrophages; Immune-to-brain signaling; Alzheimer's disease; Cerebrovascular regulation; CNS infections

Increasing evidence indicates that cells of the innate immune system, such as myeloid cells, play a critical role in the maintenance of brain homeostasis and in the mechanisms of brain diseases [1–3]. Much of the research in this area has focused on microglia, brain-resident myeloid cells, which have been implicated in a wide variety of processes in brain development, function, and disease [4]. However, considerably less is known about other innate immune cells residing in the brain, such as perivascular macrophages (PVM). PVM are myeloid cells located in the perivascular compartment surrounding arteries and veins as they penetrate deeply into the brain tissue (perivascular space or Virchow-Robin space). Although myeloid cells associated with cerebral blood vessels have been described for several decades, their origin, lineage identity, and function have not been fully elucidated. Owing to recent advances in macrophage biology and genetic approaches for cell linage

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Compliance with ethical standards

tracing, the identity of these cells and their potential functional roles are becoming better appreciated. Here, we will briefly examine these recent developments to provide an overview of the origin of PVM and to review the evidence supporting their role in brain homeostasis and disease states.

Perivascular cells and their characterization

The perivascular compartment is delimited by the vascular basement membrane on the abluminal side of the vessel wall and by the glia limitans basement membrane on the parenchymal side [5] (Fig. 1). At the level of smaller arterioles (≤ 10 μM) and capillaries, the two membranes fuse together thereby occluding the perivascular space [5]. The perivascular space contains several cell types including PVM [6, 7]. Here, we will summarize key findings that led to the identification and characterization of PVM.

Early studies

In 1980, Mato et al. showed that trypan blue and horseradish peroxidase administered in the cerebral ventricles are taken up by elongated cells in the perivascular space [8]. These cells, originally defined as granular pericytes, were later called Mato's fluorescent granular perithelial (FGP) cells and were thought to remove metabolic wastes from brain parenchyma as attested by the presence of globular vacuolated inclusions in their cytoplasm [9]. FGP cells were also able to incorporate circulating lipids, and the amount of lipid deposits in FGP cells was found to increase with age [10]. It was later shown that in normal mouse brain cortex, scavenger receptors are mainly expressed in FGP cells surrounding arterioles 10–35 μm in diameter [11]. Fluorescent-labeled acetyl-LDL, a well-known scavenger receptor ligand, as well as ferritin could be taken up by these cells [11]. FGP cells were localized to the perivascular space and, unlike pericytes, which are embedded in the endothelial basement membrane of capillaries, FGP cells were observed around arterioles and venules [12]. However, the precise identity of these cells was not defined.

From perivascular microglia to PVM

In 1988, Hickey and Kimura described perivascular cells, termed "perivascular microglial cells," that were bone marrow (BM) derived and able to present antigens to lymphocytes [13]. These cells, positive for the cell surface glycoprotein ED2, showed an elongated shape and were located around cerebral blood vessels [13]. Cells with similar characteristics were also found in association with the leptomeninges. However, Graeber et al. suggested that these $ED2^+$ perivascular cells were distinct from microglia, which are not positive for ED2 [14]. However, since these cells were surrounded by the endothelial basement membrane of capillaries [14], their pericyte identity cannot be excluded. After purification and sequencing, the ED2 antigen was identified as CD163, a membrane glycoprotein belonging to the scavenger receptor cystein-rich (SRCR) superfamily group B, which functions as a high affinity receptor for the hemoglobin-haptoglobin complex [15]. $CD163^+$ cells were also positive for the phagocytic marker CD68 and negative for smooth muscle actin, confirming that these perivascular cells were macrophages and not pericytes or smooth muscle cells [16, 17]. In addition, $CD163^+$ cells were positive for MHC class II antigen and several co-stimulatory molecules such as CD80, CD86, and CD40, suggesting a possible role in antigen

recognition and presentation [16]. These findings, collectively, established PVM as a distinct population of myeloid cells located in the perivascular space surrounding cerebral blood vessels.

Towards a molecular and functional characterization of PVM

In the mouse brain, PVM are also enriched with the mannose receptor (CD206) [18, 19]. CD206 is expressed by specific macrophage subpopulations [20] and is involved in pathogen recognition and receptor-mediated endocytosis [21]. CD206 expression is observed in PVM, meningeal macrophages (MGM), and choroid plexus macrophages (CPM) but is not present in microglia [22] or leukocytes infiltrating the brain parenchyma (Table 1) [18]. Unlike CD163, CD206 is not expressed in infiltrating monocytes, indicating that it is a more specific marker of PVM [23]. CD45 expression levels are higher in PVM compared to microglia [22], which can be used to differentiate these cell types using flow cytometry [22]. All brain-resident myeloid cells express the genes encoding the fractalkine receptor (Cx3cr1) or the receptor for the macrophage colony-stimulating factor 1 (Csf1r) and Aif1 (Iba-1) [22]. However, controversial data still exist concerning the expression of Cx3cr1 and Iba-1 in PVM. In some studies using immunostaining, PVM were found to express lower levels of both Cx3cr1 and Iba-1 compared to microglia [19, 24]. However, Goldman et al. reported that Cx3cr1 RNA levels were lower in PVM compared to microglia whereas Iba1 RNA levels were not different in the two cell populations [22]. This discrepancy needs to be resolved.

MGM share the PVM's transcriptional profile and also express CD169, CD11c, and CD68 [24]. Single-cell RNA-seq confirmed that PVM can be distinguished from microglia by the expression of CD206 and CD36 and of the lymphatic vessel endothelial hyaluronan receptor-1 (Lyve1) [25] [22], whereas microglia characteristically express higher levels of the purinergic receptor P2ry12 and hexosaminidase-b (Hexb) than PVM [22]. PVM can also be labeled and identified by intracerebroventricular (icv) injection of tracers such as fluorescent-labeled dextran, which is phagocytosed by PVM leading to a granular labeling pattern reflecting intracellular storage in phagosomes [26, 27, 17, 19, 28].

The study of the function of PVM in health and disease has been facilitated by the use of clodronate (CLO)-containing liposomes [29]. CLO liposomes injected into the cerebral ventricles are phagocytized by PVM and MGM. Once in the cytosol, CLO acts as a cytotoxic ATP analog, which impairs mitochondrial oxygen consumption leading to cell death [30]. In the adult brain, icv injection of CLO depletes both PVM and MGM without affecting microglial cells or peripheral mononuclear cells [19], except for a transient reduction in the number of Kupffer cells in the liver [29]. However, the depletion is transient, and PVM and MGM start to reappear 14 days after CLO injection [29]. The source of repopulating PVM and MGM has not been determined, and it remains unclear if the repopulation occurs from circulating myeloid cells or from brain-resident precursors. Nevertheless, as discussed later in this review, CLO has been a useful tool to study the role of PVM in health and disease and has complemented the results obtained with replacement of PVM using BM chimeras (Table 2).

Where do brain perivascular macrophages come from?

The origin of PVM is still being debated. Hickey and Kimura suggested that PVM were BM derived and continuously replaced by blood monocytes [13]. Some studies took advantage of the ability of PVM to phagocytize dextran to investigate the turnover of PVM [17, 28]. Fluorescein-conjugated dextran was injected into the CSF, and biotin- or rhodamine-labeled dextran was injected 1 or 4 weeks later, respectively. Animals were then sacrificed 4 to 24 h after the second injection. The two injections allowed for the identification of two PVM populations: “older” PVM that had taken up both dyes and “new” macrophages labeled only with the second dye. These studies revealed that, after 1 month, approximately 6% of PVM were single positive for the second dye injected, i.e., “new” macrophages [17, 28]. Both the single- and double-labeled cells were CD163 positive [17]. These data provided evidence that PVM are continuously turned over, albeit at a relatively slow rate, but the source of the new PVM could not be determined.

Early BM chimera studies in rodents supported the existence of continuous trafficking of PVM from the circulation into the brain and suggested that approximately 10% of PVM are replaced from BM-derived monocytes every month [31]. In subsequent studies, BM cells expressing the green fluorescent protein (GFP) were transplanted into adult mice [32]. These studies showed that 2–3 months after the transplant, the majority of GFP^+ cells in the brain were also $CD45^+$, had an elongated shape, and were localized in close proximity to cerebral blood vessels, particularly those penetrating the cerebral cortex [19, 32]. However, some of the GFP^+ cells were also $Iba\text{-}1^+$ and had a ramified morphology undistinguishable from that of microglia. These cells were not associated with vessel and their number increased with time [32].

More recently, it has become evident that some of the findings in BM chimeras have to be interpreted with caution due to the brain alterations induced by brain irradiation. Brain irradiation disrupts the blood brain barrier (BBB) and induces pro-inflammatory mediators, facilitating the recruitment of BM-derived monocytes into the brain parenchyma [33]. In contrast, in BM chimeras in which the brain was protected from irradiation by head shielding, monocytes failed to enter the brain parenchyma and BM-derived microglia-like cells were not observed [34]. Similarly, a number of engrafted cells in brain parenchyma were drastically reduced in mice in which BM ablation was induced by administration of the alkylating agent busulfan instead of irradiation, an effect that could not be attributed to insufficient chimerism [33]. Other studies also support the idea that PVM and MGM are not replaced by circulating monocytes [22]. These studies used $Cx3cr1Cre^{ER}$ mice expressing a Cre-ERT2 fusion protein under the control of the endogenous Cx3cr1 promoter. As mentioned above, the fractalkine receptor Cx3cr1 is expressed in all brain-resident myeloid cells including microglia, CPM, PVM, and MGM. When $Cx3cr1Cre^{ER}$ mice are bred with mice containing loxP-flanked STOP cassette upstream of the yellow fluorescent protein (YFP) sequence, cre-mediated recombination induced by tamoxifen results in YFP expression in $Cx3Cr1^+$ cells ($Cx3Cr1^{ER}$Rosa26-YFP) [22]. In this study, tamoxifen was injected at embryonic day 9 in pregnant mice to generate $Cx3cr1Cre^{ER}$Rosa26-YFP embryos. The injection of tamoxifen induced irreversible expression of YFP in Cx3cr1-expressing cells and their progeny. By using this approach, the authors were able to

demonstrate that YFP$^+$ CPM, PVM, and MGM are present in the embryonic brain [22]. Immunoelectron microscopy confirmed that YFP-expressing cells are located in the perivascular space [22]. Considering that at this developmental stage, hematopoietic lineage providing blood cells after birth has not yet developed, it can be assumed that all Cx3cr1-expressing cells derive from erythromyeloid precursors in the yolk sack, the major source of hematopoietic embryonic cells. Furthermore, YFP$^+$ PVM and MGM retained the YFP label in 6-week-old mice, demonstrating that embryonic labeling persisted into adulthood [22]. Tamoxifen treatment of adult Cx3cr1Cre^{ER}Rosa26-YFP mice showed long-term YFP labeling of PVM and MGM, suggesting that these two subpopulations are stable and are not replaced by blood monocytes, while CPM showed a higher turnover rate [22]. This conclusion was also reached on the basis of parabiosis experiments, in which WT- and GFP-expressing mice were surgically connected for several months. These experiments failed to demonstrate GFP$^+$ PVM and MGM [22], supporting the idea that they are not replaced by blood monocytes. Furthermore, Myb, an essential transcription factor for hematopoietic stem cell development in the BM, was found not to be required for PVM development [22]. Taken together, these studies suggest that PVM are likely to be part of the Myb-independent macrophages generated from yolk sac progenitors early in development [35].

Pathophysiological role of perivascular macrophages

Increasing evidence indicates that PVM are involved in a wide variety of pathological states in the brain. These are briefly reviewed in the following sections and summarized in Table 2.

Alzheimer’s disease pathology

Alzheimer’s disease (AD), the major cause of age-related dementia, is characterized pathologically by accumulation of the amyloid-β (Aβ) peptide in the brain (amyloid plaques) and cerebral blood vessels (cerebral amyloid angiopathy) [36]. Enriched with scavenger receptors, PVM may be involved in the clearance of waste products from the cerebral parenchyma [11, 37]. In mice expressing a mutant form of the amyloid precursor protein (APP) (TgCRND8 mice), a model of cerebral amyloid accumulation, depletion of PVM by CLO increased the deposition of amyloid-β around cerebral blood vessels [38], whereas amyloid plaques in the brain parenchyma were not affected. In another study [39], it was shown that PVM express scavenger receptor class B type I (SR-BI), a high-density lipoprotein receptor that regulates cholesterol efflux from the peripheral tissues to the liver [40]. SR-BI$^+$ PVM were observed in association with amyloid deposits on meningeal and cortical blood vessels in J20 mice [39], a transgenic mouse expressing mutated APP [41]. Deletion of SR-BI increased vascular and parenchymal amyloid deposition in the hippocampus and exacerbated behavioral deficits of J20 mice [39]. These data implicate SR-BI in PVM in the vascular and parenchymal Aβ clearance [39] and, in concert with the CLO data [38], provide further evidence for the involvement of PVM in Aβ trafficking and disposal from the brain.

Recent data suggest that PVM may also contribute to the deleterious effects of Aβ on the regulation of cerebral blood flow, which is thought to contribute to the mechanisms of cognitive dysfunction in AD [42]. Aβ impairs the increase in cerebral blood flow produced

by neural activity and induces endothelial dysfunction, effects dependent on vascular oxidative stress produced by a Nox2-containing NADPH oxidase [42]. Selective depletion of PVM abrogated the vascular oxidative stress and neurovascular alterations induced by Aβ either applied directly to the neocortex of wild-type mice or produced endogenously in Tg2576 mice overexpressing mutated APP [43]. PVM were also needed for the neurovascular dysfunction induced by circulating Aβ, an effect mediated by Aβ entering the perivascular space and reaching PVM to induce vascular oxidative stress [43]. The cerebrovascular dysfunction was abolished in Tg2576 mice transplanted with CD36- or Nox2-deficient BM [43]. Furthermore, transplant of CD36+ BM reinstated the neurovascular dysfunction induced by Aβ in CD36-deficient mice [43], suggesting that the CD36-Nox2 signaling pathway in PVM is required for the deleterious cerebrovascular effects of Aβ. These findings, collectively, could implicate PVM in AD pathophysiology and suggest that PVM scavenger receptors, including SR-BI or CD36, are crucial in modulating the accumulation of Aβ in the brain and related neurovascular effects.

Vascular permeability

Consistent with their involvement in vascular permeability in systemic vessels [44], PVM may also play a role in the movement of solutes, infectious agents, and immune cells from the blood to the brain. For example, in the area postrema, a circumventricular organ devoid of BBB, PVM restrict the entry of tracers larger than 10 kDa [45]. In addition, in the mouse retina, PVM move along retinal blood vessels and accumulate blood-borne molecules without disruption of the blood-retina barrier [46]. In experimental and human retinopathy, in which the barrier is disrupted, PVM migrate to the lesion site and may play a role in limiting the leakage of blood components into the retina [46].

CNS infections

In a rat model of streptococcal meningitis, CLO treatment was associated with worsening of symptoms and higher bacteria load in the CSF, an effect attributed to a reduction of the influx of neutrophil into the brain parenchyma [47]. In contrast, PVM and MGM may play a protective role in bacterial meningitis by promoting the influx of neutrophils into the brain needed to counteract the invading bacteria (Fig. 2) [47]. Similarly, PVM depletion is beneficial in the encephalitis induced by intranasal application of vesicular stomatitis virus (VSV) [48]. Thus, PVM and MGM depletion by CLO suppressed the brain accumulation of neutrophils and T cells, reduced VSV load, and improved motor deficits [48].

PVM have been implicated in the pathogenesis of the encephalitis associated with human immunodeficiency virus (HIV) infection. Around 60% of people infected with HIV develop evidence of neurological dysfunction, and 30–40% develop severe cognitive deficits (AIDS-dementia complex) [49]. Increasing evidence suggests that PVM are the major cell population infected by HIV or simian immunodeficiency virus (SIV), a primate model of AIDS [50]. Both SIV RNA and the viral glycoprotein gp120 are found in PVM of animals infected by SIV, with minor contribution from parenchymal microglia or T lymphocytes and no evidence of infection in endothelial cells and astrocytes [50]. Based on these observations, it was proposed that the virus might enter the CNS in infected monocytes destined to become PVM [49]. However, over 80% of the PVM in the lesions are present in

the brain before development of pathology, suggesting that brain-resident PVM, rather than peripheral monocytes recruited into the lesion, are targeted by the infection [51]. In this context, cells expressing Ki-67, a marker of cell proliferation, were found in SIV lesions [52]. The majority of these cells were $CD163^+$ and were localized perivascularly [52]. Therefore, proliferation of PVM, rather than recruitment of monocytes from the periphery, could be the primary mechanism of encephalitic lesion formation and persistence of the viral reservoir in the brain [52].

Multiple sclerosis

PVM are increased in number in active multiple sclerosis lesions and are positive for myelin basic protein and for the major histocompatibility complex HLA-DR suggesting that they could process and present antigens [53]. In acute experimental allergic encephalomyelitis (EAE) in rat, a model of multiple sclerosis, the number of PVM increased before disease onset, and their depletion ameliorates neurological symptoms [54]. Although the mechanisms of this effect are not clear, PVM may act as antigen-presenting cells and reactivate T cells once they cross the BBB to infiltrate the brain [54]. In addition, PVM may exacerbate EAE by promoting monocyte recruitment through the expression of chemokines such as MCP-1 (monocyte chemoattractant protein) and MIP-1α (macrophage inflammatory protein 1α) [55].

Hypothalamic-pituitary axis and neurohumoral activation

PVM have been implicated in the activation of the hypothalamic-pituitary-adrenal (HPA) axis in a wide variety of settings. Systemic inflammation is associated with activation of the HPA axis and fever, responses requiring the prostaglandin E_2 (PGE_2) [56]. Systemic administration of IL-1β or lipopolysaccharide (LPS) increases cyclooxygenase-2 (COX-2) and the microsomal PGE_2 synthase, one of the terminal enzymes in PGE_2 synthesis, in cerebral endothelial cells [57]. In turn, PGE_2 release is responsible for the activation of the HPA axis, leading to release of the stress hormones ACTH and corticosterone and induction of fever. This response involves the crosstalk between PVM and cerebral endothelial cells but depends critically on the characteristics of the inflammatory stimulus [58]. For example, in IL1β-induced systemic inflammation, PVM depletion suppresses the increase in endothelial COX-2 and PGE_2 and the HPA activation, whereas in LPS-induced inflammation, PVM depletion enhances this response [59]. Therefore, PVM may promote or suppress the HPA axis activation induced by systemic inflammation depending on the nature and complexity of the inflammatory stimulus [60].

The HPA axis can also be activated by emotional stress. Restraint stress in rat induced COX-2 expression in PVM and increased both brain PGE_2 and the number of activated neurons in the hypothalamic paraventricular nucleus (PVN) [61], wherein parvocellular neurosecretory neurons regulate the HPA axis [62]. These responses were greatly diminished by PVM depletion. There is also evidence that PVM are involved in the neurohumoral and inflammatory responses induced by myocardial infarction (MI). MI in rat increases circulating levels of TNF and IL-1β, as well as norepinephrine, suggesting sympathetic activation [63]. The effect is associated with increased COX-2 expression in the PVN, resulting in increased levels of PGE_2 in the cerebrospinal fluid. PVM depletion does not

affect the increase in circulating cytokines induced by MI but abrogates COX-2 upregulation and sympathetic activation, implicating PVM in the mechanisms of post-MI neurohumoral activation [63]. Consistent with this conclusion, systemic administration of TNF induces COX-2 expression in PVM and sympathetic activation via COX-2-dependent mechanisms [63]. These data, collectively, raise the possibility that PVM, through COX-2 induction and PGE_2, may sense peripheral signals in the circulation and translate them into neurohumoral responses.

Cerebrovascular risk factors and cognitive impairment

PVM have recently been implicated in the cerebrovascular and neurocognitive alterations induced by arterial hypertension. Hypertension induces changes in the structure of cerebral blood vessels leading to a reduction in vascular diameter (hypertrophy and remodeling) [64]. It also alters neurovascular regulatory mechanisms, such as the increase in cerebral blood flow (CBF) produced by endothelium-dependent vasodilators or by neural activity, leading to cognitive dysfunction [64]. These effects are, for the most part, mediated by reactive oxygen species (ROS) produced by a NOX2-containing NADPH oxidase [65]. PVM depletion in stroke-prone spontaneously hypertensive rats offsets some of the changes in vascular structure induced by chronic hypertension and ameliorates the vasodilatation induced by acetylcholine, an endothelium-dependent vasodilator [66]. In a mouse model of hypertension induced by systemic administration of sub-pressor doses of angiotensin-2 (AngII) for 2 weeks, we found that PVM depletion does not affect the elevation of blood pressure but ameliorates the impairment of the increase in CBF induced by neural activity and acetylcholine [19]. Next, we set out to determine if PVM are the cells expressing AT1R and NOX2 responsible for the dysfunction. After demonstrating that AngII crosses the BBB and reaches PVM, we used BM chimeras to replace wild-type PVM with PVM lacking the AngII type 1 receptor (AT1R) or NOX2. We found that AngII engages AT1R in PVM and activates NOX2 in these cells leading to the vascular oxidative stress responsible for the neurovascular dysfunction associated with hypertension. To determine whether the improvement in neurovascular function afforded by PVM depletion is associated with the improvement of cognitive function, we used BPH mice, a genetic model of chronic hypertension [67]. BPH mice exhibited neurovascular dysfunction dependent on circulating AngII, AT1R, and vascular oxidative stress [19], which was counteracted by PVM depletion [19]. Using the “novel object recognition test” and the “Barnes maze test,” well-established tasks exploring hippocampal function in mice, we found that the rescue of neurovascular function produced by PVM depletion was associated with a marked improvement in cognitive function [19]. These findings establish a key role of PVM in the neurovascular and cognitive dysfunction associated with hypertension.

Accumulation of $CD163^+$ cells around cerebral blood vessels has been shown in autopsy samples of patients with traumatic brain injury, intracerebral hemorrhage, focal cerebral ischemia, and hypoxic encephalopathy [68]. Their number increases over time and is observed even in patients with chronic lesions [68]. However, since no further characterization was performed, it is not clear whether these cells are blood-derived monocytes or PVM. $CD163^+$ cells increase over time also in a rat model of traumatic brain

injury [69], but the identity of these cells has not been defined, and the role of PVM remains to be established.

In mice fed a high-fat diet (HFD), macrophages may have a protective role. HFD initially reduces GLUT1 expression in brain vascular endothelial cells thereby reducing brain glucose uptake [70]. However, the suppression of endothelial GLUT1 is transient and is restored upon prolonged HFD, a response dependent on a compensatory VEGF production by myeloid cells, including PVM. In support of this hypothesis, selective ablation of VEGF in myeloid cells, by crossing VEGF “floxed” mice with lysozyme-CRE driver mice, reduced endothelial GLUT1 and brain glucose uptake. Interestingly, ablation of VEGF in myeloid cells impaired brain glucose uptake and worsened the memory dysfunction in mice overexpressing mutated APP (APP-PS1) fed a HFD. However, this study raises the caveat that, by using lysozyme-CRE driver mice, VEGF was deleted in all myeloid cells. Consequently, the contribution of circulating monocytes and microglia to the findings cannot be excluded.

Future directions

Much has been learned about the origin, localization, and function of brain PVM, but several questions remain to be addressed. For example, it remains unclear if the self-renewal of PVM takes place through brain-resident progenitors and, if so, the identity of these cells and their relationships to microglia and other brain-resident macrophage populations remain to be defined. Microglial turnover varies regionally and results from a stochastic cell division process in homeostatic conditions and from expansion of selected clones after local microglial proliferation caused by facial nerve transection [71]. It remains unclear if similar processes of self-renewal and expansion, independent of a precursor pool, also are involved in PVM turnover and proliferation. The molecular factors driving PVM development, migration, and perivascular targeting have not been identified and a specific molecular signature of PVM has yet to be provided. The majority of studies investigating the role of PVM in diseases used CLO. However, since CLO depletes both MGM and PVM, the observed effects cannot be attributed exclusively to PVM. Considering the emerging role of meningeal immune cells in brain function [72], more detailed studies are needed to elucidate the relative contribution of PVM and MGM in health and disease. Furthermore, the changes that brain diseases induce in PVM and the molecular determinants driving their beneficial or deleterious effects on disease outcome remain unclear. Finally, although PVM can exert deleterious effects by producing reactive oxygen species, other potential pathogenic factors remain to be defined. Elucidating some of these questions may provide insight into how to target PVM for therapeutic purposes. Considering the growing evidence linking these cells to neurodegenerative, neurovascular, infectious, and neuroimmune diseases, PVM would constitute a valuable therapeutic target to protect the brain from a wide variety of highly prevalent and devastating diseases.

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References

1. Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. Nat Immunol. 2017; 18:123–131. [PubMed: 28092374]
2. Herz J, Filiano AJ, Smith A, Yogev N, Kipnis J. Myeloid cells in the central nervous system. Immunity. 2017; 46:943–956. [PubMed: 28636961]
3. Prinz M, Erny D, Hagemeyer N. Ontogeny and homeostasis of CNS myeloid cells. Nat Immunol. 2017; 18:385–392. [PubMed: 28323268]
4. Saijo K, Glass CK. Microglial cell origin and phenotypes in health and disease. Nat Rev Immunol. 2011; 11:775–787. [PubMed: 22025055]
5. Ransohoff RM, Engelhardt B. The anatomical and cellular basis of immune surveillance in the central nervous system. Nat Rev Immunol. 2012; 12:623–635. [PubMed: 22903150]
6. Zhang ET, Inman CB, Weller RO. Interrelationships of the pia mater and the perivascular (Virchow-Robin) spaces in the human cerebrum. J Anat. 1990; 170:111–123. [PubMed: 2254158]
7. Galanternik MV, Castranova D, Gore AV, Blewett NH, Jung HM, Stratman AN, Kirby MR, Iben J, Miller MF, Kawakami K, et al. A novel perivascular cell population in the zebrafish brain. Elife. 2017; doi: 10.7554/eLife.24369
8. Mato M, Ookawara S, Kurihara K. Uptake of exogenous substances and marked infoldings of the fluorescent granular pericyte in cerebral fine vessels. Am J Anat. 1980; 157:329–332. [PubMed: 7405872]
9. Mato M, Aikawa E, Mato TK, Kurihara K. Tridimensional observation of fluorescent granular perithelial (FGP) cells in rat cerebral blood vessels. Anat Rec. 1986; 215:413–419. [PubMed: 3740477]
10. Mato M, Ookawara S, Sano M, Fukuda S. Uptake of fat by fluorescent granular perithelial cells in cerebral cortex after administration of fat rich chow. Experientia. 1982; 38:1496–1498. [PubMed: 7151978]
11. Mato M, Ookawara S, Sakamoto A, Aikawa E, Ogawa T, Mitsuhashi U, Masuzawa T, Suzuki H, Honda M, Yazaki Y, et al. Involvement of specific macrophage-lineage cells surrounding arterioles in barrier and scavenger function in brain cortex. Proc Natl Acad Sci U S A. 1996; 93:3269–3274. [PubMed: 8622926]
12. Ookawara S, Mitsuhashi U, Suminaga Y, Mato M. Study on distribution of pericyte and fluorescent granular perithelial (FGP) cell in the transitional region between arteriole and capillary in rat cerebral cortex. Anat Rec. 1996; 244:257–264. [PubMed: 8808400]
13. Hickey WF, Kimura H. Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. Science. 1988; 239:290–292. [PubMed: 3276004]
14. Graeber MB, Streit WJ, Kreutzberg GW. Identity of ED2-positive perivascular cells in rat brain. J Neurosci Res. 1989; 22:103–106. [PubMed: 2926837]
15. Fabriek BO, Polfliet MMJ, Vloet RPM, van der Schors RC, Ligtenberg AJ, Weaver LK, Geest C, Matsuno K, Moestrup SK, Dijkstra CD, et al. The macrophage CD163 surface glycoprotein is an erythroblast adhesion receptor. Blood. 2007; 109:5223–5229. [PubMed: 17353345]
16. Fabriek BO, Van Haastert ES, Galea I, Polfliet MM, Döpp ED, Van Den Heuvel MM, Van Den Berg TK, De Groot CJ, Van Der Valk P, Dijkstra CD. CD163-positive perivascular macrophages in the human CNS express molecules for antigen recognition and presentation. Glia. 2005; 51:297–305. [PubMed: 15846794]
17. Kim W-K, Alvarez X, Fisher J, Bronfin B, Westmoreland S, McLaurin J, Williams K. CD163 identifies perivascular macrophages in normal and viral encephalitic brains and potential precursors to perivascular macrophages in blood. Am J Pathol. 2006; 168:822–834. [PubMed: 16507898]
18. Galea I, Palin K, Newman TA, Van Rooijen N, Perry VH, Boche D. Mannose receptor expression specifically reveals perivascular macrophages in normal, injured, and diseased mouse brain. Glia. 2004; 49:375–384.

19. Faraco G, Sugiyama Y, Lane D, Garcia-Bonilla L, Chang H, Santisteban MM, Racchumi G, Murphy M, Van Rooijen N, Anrather J, et al. Perivascular macrophages mediate the neurovascular and cognitive dysfunction associated with hypertension. J Clin Invest. 2016; 126:4674–4689. [PubMed: 27841763]
20. Linehan SA, Stahl PD, Gordon S. Mannose receptor and its putative ligands in normal murine lymphoid and nonlymphoid organs: in situ expression of mannose receptor by selected macrophages, endothelial cells, perivascular microglia, and mesangial cells, but not dendritic cells. J Exp Med. 1999; 189:1961–1972. [PubMed: 10377192]
21. Linehan SA, Martinez-Pomares L, Gordon S. Mannose receptor and scavenger receptor: two macrophage pattern recognition receptors with diverse functions in tissue homeostasis and host defense. Adv Exp Med Biol. 2000; 479:1–14. [PubMed: 10897405]
22. Goldmann T, Wieghofer P, Jordão MJC, Prutek F, Hagemeyer N, Frenzel K, Amann L, Staszewski O, Kierdorf K, Krueger M, et al. Origin, fate and dynamics of macrophages at central nervous system interfaces. Nat Immunol. 2016; 17:797–805. [PubMed: 27135602]
23. Holder GE, McGary CM, Johnson EM, Zheng R, John VT, Sugimoto C, Kuroda MJ, Kim WK. Expression of the man-nose receptor CD206 in HIV and SIV encephalitis: a phenotypic switch of brain perivascular macrophages with virus infection. J NeuroImmune Pharmacol. 2014; 9:716–726. [PubMed: 25146376]
24. Chinnery HR, Ruitenberg MJ, McMenamin PG. Novel characterization of monocyte-derived cell populations in the meninges and choroid plexus and their rates of replenishment in bone marrow chimeric mice. J Neuropathol Exp Neurol. 2010; 69:896–909. [PubMed: 20720507]
25. Zeisel A, Muñoz-Manchado AB, Codeluppi S, Lönnerberg P, La Manno G, Juréus A, Marques S, Munguba H, He L, Betsholtz C, et al. Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. Science. 2015; 347:1138–1142. [PubMed: 25700174]
26. Bechmann I, Priller J, Kovac A, Böntert M, Wehner T, Klett FF, Bohsung J, Stuschke M, Dirnagl U, Nitsch R. Immune surveillance of mouse brain perivascular spaces by blood-borne macrophages. Eur J Neurosci. 2002; 14:1651–1658.
27. del Rey A, Balschun D, Wetzel W, Randolf A, Besedovsky HO. A cytokine network involving brain-borne IL-1β, IL-1ra, IL-18, IL-6, and TNFα operates during long-term potentiation and learning. Brain Behav Immun. 2013; 33:15–23. [PubMed: 23747799]
28. Bechmann I, Kwidzinski E, Kovac AD, Simbürger E, Horvath T, Gimsa U, Dirnagl U, Priller J, Nitsch R. Turnover of rat brain perivascular cells. Exp Neurol. 2001; 168:242–249. [PubMed: 11259112]
29. Polfliet MM, Goede PH, van Kesteren-Hendrikx EM, van Rooijen N, Dijkstra CD, van den Berg TK. A method for the selective depletion of perivascular and meningeal macrophages in the central nervous system. J Neuroimmunol. 2001; 116:188–195. [PubMed: 11438173]
30. Lehenkari PP, Kellinsalmi M, Näpänkangas JP, Ylitalo KV, Mönkkönen J, Rogers MJ, Azhayev A, Väänänen HK, Hassinen IE. Further insight into mechanism of action of clodronate: inhibition of mitochondrial ADP/ATP translocase by a nonhydrolyzable, adenine-containing metabolite. Mol Pharmacol. 2002; 61:1255–1262. [PubMed: 11961144]
31. Hickey WF, Vass K, Lassmann H. Bone marrow-derived elements in the central nervous system: an immunohistochemical and ultrastructural survey of rat chimeras. J Neuropathol Exp Neurol. 1992; 51:246–256. [PubMed: 1583531]
32. Vallières L, Sawchenko PE. Bone marrow-derived cells that populate the adult mouse brain preserve their hematopoietic identity. J Neurosci. 2003; 23:5197–5207. [PubMed: 12832544]
33. Kierdorf K, Katzmarski N, Haas CA, Prinz M. Bone marrow cell recruitment to the brain in the absence of irradiation or parabiosis bias. PLoS One. 2013; 8:e58544. [PubMed: 23526995]
34. Mildner A, Schmidt H, Nitsche M, Merkler D, Hanisch UK, Mack M, Heikenwalder M, Brück W, Priller J, Prinz M. Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under defined host conditions. Nat Neurosci. 2007; 10:1544–1553. [PubMed: 18026096]
35. Perdiguero EG, Geissmann F. Myb-independent macrophages: a family of cells that develops with their tissue of residence and is involved in its homeostasis. Cold Spring Harb Symp Quant Biol. 2013; 78:91–100. [PubMed: 24122769]

36. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. Cell. 2016; 164:603–615. [PubMed: 26871627]
37. Kida S, Steart PV, Zhang ET, Weller RO. Perivascular cells act as scavengers in the cerebral perivascular spaces and remain distinct from pericytes, microglia and macrophages. Acta Neuropathol. 1993; 85:646–652. [PubMed: 8337943]
38. McLaurin J, Hawkes C. Selective targeting of perivascular macrophages for β-amyloid clearance in cerebral amyloid angiopathy. Alzheimers Dement. 2009; 5:152.
39. Thanopoulou K, Fragkouli A, Stylianopoulou F, Georgopoulos S. Scavenger receptor class B type I (SR-BI) regulates perivascular macrophages and modifies amyloid pathology in an Alzheimer mouse model. Proc Natl Acad Sci U S A. 2010; 107:20816–20821. [PubMed: 21076037]
40. Steinberg D. A docking receptor for HDL cholesterol esters. Science. 1996; 271:460–461. [PubMed: 8560256]
41. Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, et al. High-level neuronal expression of abeta 1–42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci. 2000; 20:4050–4058. [PubMed: 10818140]
42. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci. 2004; 5:347–360. [PubMed: 15100718]
43. Park L, Uekawa K, Garcia-Bonilla L, Koizumi K, Murphy M, Pistik R, Younkin L, Younkin S, Zhou P, Carlson G, et al. Brain perivascular macrophages initiate the neurovascular dysfunction of Alzheimer Aβ peptides. Circ Res. 2017; doi: 10.1161/CIRCRESAHA.117.311054
44. He H, Mack JJ, Güç E, Warren CM, Squadrito ML, Kilarski WW, Baer C, Freshman RD, McDonald AI, Ziyad S, et al. Perivascular macrophages limit permeability. Arterioscler Thromb Vasc Biol. 2016; 36:2203–2212. [PubMed: 27634833]
45. Willis CL, Garwood CJ, Ray DE. A size selective vascular barrier in the rat area postrema formed by perivascular macrophages and the extracellular matrix. Neuroscience. 2007; 150:498–509. [PubMed: 17945430]
46. Mendes-Jorge L, Ramos D, Luppo M, Llombart C, Alexandre-Pires G, Nacher V, Melgarejo V, Correia M, Navarro M, Carretero A, et al. Scavenger function of resident autofluorescent perivascular macrophages and their contribution to the maintenance of the blood-retinal barrier. Invest Ophthalmol Vis Sci. 2009; 50:5997–6005. [PubMed: 19608545]
47. Polfliet MM, Zwijnenburg PJ, van Furth AM, van der Poll T, Döpp EA, Renardel de Lavalette C, van Kesteren-Hendrikx EM, van Rooijen N, Dijkstra CD, van den Berg TK. Meningeal and perivascular macrophages of the central nervous system play a protective role during bacterial meningitis. J Immunol. 2001; 167:4644–4650. [PubMed: 11591794]
48. Steel CD, Kim W-K, Sanford LD, Wellman LL, Burnett S, Van Rooijen N, Ciavarra RP. Distinct macrophage subpopulations regulate viral encephalitis but not viral clearance in the CNS. J Neuroimmunol. 2010; 226:81–92. [PubMed: 20599280]
49. Williams KC, Hickey WF. Central nervous system damage, monocytes and macrophages, and neurological disorders in AIDS. Annu Rev Neurosci. 2002; 25:537–562. [PubMed: 12052920]
50. Williams KC, Corey S, Westmoreland SV, Pauley D, Knight H, deBakker C, Alvarez X, Lackner AA. Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques: implications for the neuropathogenesis of AIDS. J Exp Med. 2001; 193:905–915. [PubMed: 11304551]
51. Nowlin BT, Burdo TH, Midkiff CC, Salemi M, Alvarez X, Williams KC. SIV encephalitis lesions are composed of CD163(+) macrophages present in the central nervous system during early SIV infection and SIV-positive macrophages recruited terminally with AIDS. Am J Pathol. 2015; 185:1649–1665. [PubMed: 25963554]
52. Filipowicz AR, McGary CM, Holder GE, Lindgren AA, Johnson EM, Sugimoto C, Kuroda MJ, Kim WK. Proliferation of perivascular macrophages contributes to the development of encephalitic lesions in HIV-infected humans and in SIV-infected macaques. Sci Rep. 2016; 6:32900. [PubMed: 27610547]

53. Zhang Z, Zhang Z-Y, Schittenhelm J, Wu Y, Meyermann R, Schluesener HJ. Parenchymal accumulation of CD163+ macrophages/microglia in multiple sclerosis brains. J Neuroimmunol. 2011; 237:73–79. [PubMed: 21737148]
54. Polfliet MMJ, van de Veerdonk F, Döpp EA, van Kesteren-Hendrikx EM, van Rooijen N, Dijkstra CD, van den Berg TK. The role of perivascular and meningeal macrophages in experimental allergic encephalomyelitis. J Neuroimmunol. 2002; 122:1–8. [PubMed: 11777538]
55. Hofmann N, Lachnit N, Streppel M, Witter B, Neiss WF, Guntinas-Lichius O, Angelov DN. Increased expression of ICAM-1, VCAM-1, MCP-1, and MIP-1 alpha by spinal perivascular macrophages during experimental allergic encephalomyelitis in rats. BMC Immunol. 2002; 3:11. [PubMed: 12196270]
56. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. Physiol Rev. 1999; 79:1–71. [PubMed: 9922367]
57. Elmquist JK, Breder CD, Sherin JE, Scammell TE, Hickey WF, Dewitt D, Saper CB. Intravenous lipopolysaccharide induces cyclooxygenase 2-like immunoreactivity in rat brain perivascular microglia and meningeal macrophages. J Comp Neurol. 1997; 381:119–129. [PubMed: 9130663]
58. Vasilache AM, Qian H, Blomqvist A. Immune challenge by intraperitoneal administration of lipopolysaccharide directs gene expression in distinct blood-brain barrier cells toward enhanced prostaglandin E(2) signaling. Brain Behav Immun. 2015; 48:31–41. [PubMed: 25678162]
59. Serrats J, Schiltz JC, García-Bueno B, van Rooijen N, Reyes TM, Sawchenko PE. Dual roles for perivascular macrophages in immune-to-brain signaling. Neuron. 2010; 65:94–106. [PubMed: 20152116]
60. Schiltz JC, Sawchenko PE. Distinct brain vascular cell types manifest inducible cyclooxygenase expression as a function of the strength and nature of immune insults. J Neurosci. 2002; 22:5606–5618. [PubMed: 12097512]
61. Serrats J, Grigoleit J-S, Alvarez-Salas E, Sawchenko PE. Pro-inflammatory immune-to-brain signaling is involved in neuroendocrine responses to acute emotional stress. Brain Behav Immun. 2017; 62:53–63. [PubMed: 28179107]
62. Antoni FA. Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. Front Neuroendocrinol. 1993; 14:76–122. [PubMed: 8387436]
63. Yu Y, Zhang Z-H, Wei S-G, Serrats J, Weiss RM, Felder RB. Brain perivascular macrophages and the sympathetic response to inflammation in rats after myocardial infarction. Hypertension. 2010; 55:652–659. [PubMed: 20142564]
64. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. Hypertension. 2013; 62:810–817. [PubMed: 23980072]
65. Capone C, Faraco G, Park L, Cao X, Davisson RL, Iadecola C. The cerebrovascular dysfunction induced by slow pressor doses of angiotensin II precedes the development of hypertension. Am J Physiol Heart Circ Physiol. 2010; 300:H397–H407. [PubMed: 20971763]
66. Pires PW, Girgla SS, McClain JL, Kaminski NE, van Rooijen N, Dorrance AM. Improvement in middle cerebral artery structure and endothelial function in stroke-prone spontaneously hypertensive rats after macrophage depletion. Microcirculation. 2013; 20:650–661. [PubMed: 23647512]
67. Schlager G. Longevity in spontaneously hypertensive mice. Exp Gerontol. 1981; 16:325. [PubMed: 7318964]
68. Holfelder K, Schittenhelm J, Trautmann K, Haybaeck J, Meyermann R, Beschorner R. De novo expression of the hemoglobin scavenger receptor CD163 by activated microglia is not associated with hemorrhages in human brain lesions. Histol Histopathol. 2011; 26:1007–1017. [PubMed: 21692033]
69. Zhang Z, Zhang Z-Y, Wu Y, Schluesener HJ. Lesional accumulation of CD163+ macrophages/microglia in rat traumatic brain injury. Brain Res. 2012; 1461:102–110. [PubMed: 22583855]
70. Jais A, Solas M, Backes H, Chaurasia B, Kleinridders A, Theurich S, Mauer J, Steculorum SM, Hampel B, Goldau J, et al. Myeloid-cell-derived VEGF maintains brain glucose uptake and limits cognitive impairment in obesity. Cell. 2016; 165:882–895. [PubMed: 27133169]

71. Tay TL, Mai D, Dautzenberg J, Fernández-Klett F, Lin G, Sagar DM, Drougard A, Stempfl T, Ardura-Fabregat A, et al. A new fate mapping system reveals context-dependent random or clonal expansion of microglia. Nat Neurosci. 2017; 20:793–803. [PubMed: 28414331]

72. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. Science. 2016; 353:766. [PubMed: 27540163]

73. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science. 2010; 330:841–845. [PubMed: 20966214]

74. Kierdorf K, Erny D, Goldmann T, Sander V, Schulz C, Perdiguero EG, Wieghofer P, Heinrich A, Riemke P, Hölscher C, et al. Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. Nat Neurosci. 2013; 16:273–280. [PubMed: 23334579]

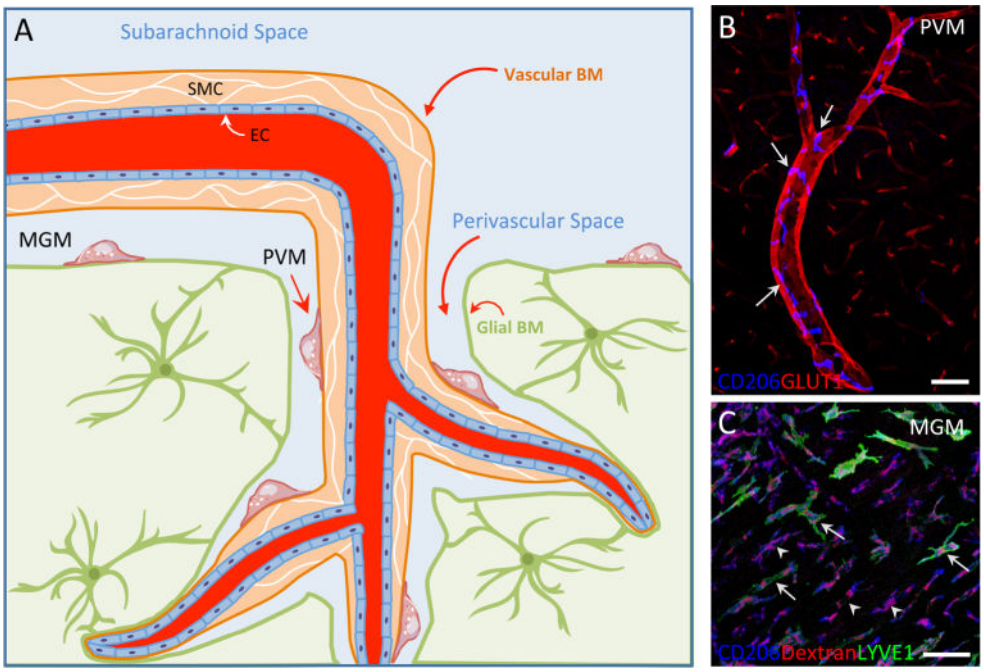

Fig. 1.

Anatomical localization of perivascular (*PVM*) and meningeal macrophages (*MGM*). **a** PVM are located in the perivascular space surrounding arteries and veins as they penetrate deeply into the brain tissue, whereas MGM can be found in association with the meninges. The perivascular space is delimited by the vascular basement membrane (*vascular BM*) on the abluminal side of the vessel wall and by the glia limitans basement membrane (*glial BM*) on the parenchymal side. At the level of smaller arterioles (≤ 10 μM) and capillaries, the two membranes fuse together occluding the perivascular space. **b** PVM can be identified as perivascular cells positive for CD206 (*arrows*). **c** Flat mount preparation of the meninges. MGM are CD206 positive and, like PVM, are able to phagocytose i.c.v-injected TRITC-dextran (*arrowheads*). MSM also express the endothelial lymphatic vessel marker LYVE1 (*arrows*). *Scale bars* 50 μM. *EC* endothelial cells, *SMC* smooth muscle cells, *i.c.v.* intracerebral ventricular

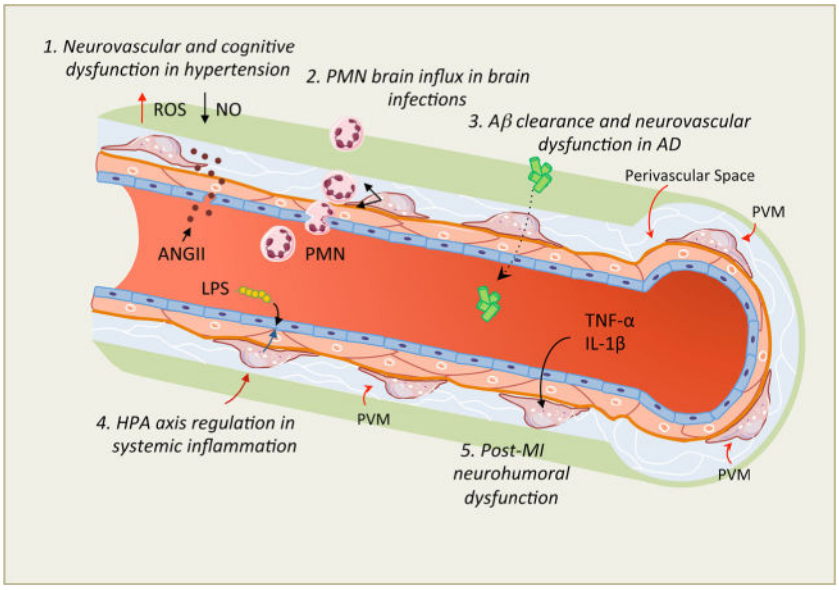

Fig. 2.

Selected roles of PVM in the brain. PVM have been implicated in (*1*) the neurovascular and cognitive dysfunction induced by hypertension, (*2*) the influx of PMN in viral and bacterial infections of the CNS, (*3*) the clearance of amyloid-β peptides and the neurovascular dysfunction in AD, (*4* and *5*) and the regulation of the HPA axis associated with systemic inflammation induced by pro-inflammatory agents, e.g., LPS, or myocardial infarction. *ROS* reactive oxygen species, *NO* nitric oxide, *PMN* polymorphonuclear cells, *ANGII* angiotensin II, *AD* Alzheimer's disease, *HPA* hypothalamic-pituitary axis, *MI* myocardial infarction

Table 1

Characteristics of brain mononuclear cells

Cell type	Embryonic origin (transcription factors)	Location	Markers	References
Perivascular macrophages	Yolk sac Fetal liver (PU.1 and Irf8 dependent, Myb and Batf3 independent)	Perivascular space	$CD206^{+}$, $CD163^{+}$, $CD45^{high}$, $CD11b^{+}$, $MHCII^{high}$, $Ly6C^{low}$, $F480^{+}$, $Cx3cr1^{low}$, $Iba1^{low}$, $LYVE1^{+}$	[19, 22, 25]
Meningeal macrophages	Yolk sac Fetal liver (PU.1 and Irf8 dependent, Myb and Batf3 independent)	Subarachnoid space and pia mater	$CD206^{+}$, $CD163^{+}$, $CD45^{high}$, $CD11b^{+}$, $MHCII^{high}$, $Ly6C^{low}$, $F480^{+}$, $Cx3cr1^{low}$, $Iba1^{low}$, $LYVE1^{+}$	[22, 24]
Choroid plexus macrophages	Yolk sac Fetal liver BM (PU. 1 dependent, Myb and Batf3 independent)	Choroid plexus	$CD206^{+}$, $CD163^{+}$, $CD45^{high}$, $CD11b^{+}$, $MHCII^{high}$, $Ly6C^{low}$, $F480^{+}$, $Cx3cr1^{low}$, $Iba1^{low}$	[22, 24]
Microglia	Yolk sac (PU. 1 and Irf8 dependent, Myb independent)	Brain parenchyma	$Iba1^{high}$, $CD206^{-}$ $CD45^{low}$, $CD163^{-}$ $CD11b^{+}$, $MHCII^{+}$, $F480^{+}$, $Cx3cr1^{high}$, $Ly6C^{-}$	[73, 74]

Table 2

Perivascular macrophages in disease models

Model	Brain region	Mode of PVM manipulation	Effect	References
Cerebral amyloid angiopathy	Neocortex, basal ganglia	Clodronate, SR-BI$^{-/-}$ mice	Promote Aβ clearance	[38, 39]
Alzheimer's Disease	Somatosensory cortex	Clodronate, BM chimeras	Mediate neurovascular dysfunction in Tg2576 mice	[43]
Viral infection	Whole brain	Clodronate	Mediate PMN and T cell brain infiltration	[48]
Meningitis	Cerebellum	Clodronate	Mediate PMN recruitment in the CSF	[47]
Multiple Sclerosis	Brain and spinal cord	Clodronate	Improvement of clinical symptoms	[54]
Systemic inflammation	Hypothalamus	Clodronate	Mediate LPS-induced HPA activation and control fever response	[59]
Emotional stress	Hypothalamus	Clodronate	Promote HPA activation and mediate emotional stress response	[61]
Myocardial infarction	Hypothalamus	Clodronate	Promote PGE_2 production and sympathetic activation	[63]
Hypertension	Somatosensory cortex 1 hippocampus	Clodronate, BM chimeras	Mediate neurovascular, cognitive dysfunction, and cerebrovascular remodeling	[19, 66]
High-fat diet	Whole brain	VEGFa$^{lox/lox}$LysM Cre$^{+/-}$ (VEGF$^{\Delta myel}$) and VEGF$^{\Delta myel}$/APP.PS 1-mice	Promote VEGF production and GLUT1 expression and mediate brain glucose uptake	[70]