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Review

Vascular dementia: A microglia's perspective

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ABSTRACT

Vascular dementia (VaD) is a second most common form of age-related dementia. It is characterized by cognitive impairment associated with vascular pathology, symptoms mainly caused by cerebral damage due to inadequate blood flow to the brain. The pathogenesis of VaD is complex, and a growing body of literature emphasizes on the involvement of microglia in disease development and progression. Here, we review the current knowledge on the role of microglia in regulating neuroinflammation under the pathogenesis of VaD. The commonly used animal and cell models for understanding the disease pathogenesis were summarized. The mechanisms by which microglia contribute to VaD are multifactorial, and we specifically focus on some of the predominant functions of microglia, including chemotaxis, secretory property, phagocytosis, and its crosstalk with other neurovascular unit cells. Finally, potential therapeutic strategies targeting microglia-modulated neuroinflammation are discussed.

1. Introduction

Vascular dementia (VaD) is an age-related neurological disease in which cognitive deficit is attributed to vascular pathology, such as ischemic stroke, hemorrhagic stroke, cerebral ischemia and hypoxia. It is known as the second most common subtype of dementia, following Alzheimer's disease (AD) (Wolters and Ikram, 2019), and is highly prevalent among elderly people in China and other Asian countries (Jhoo et al., 2008; Jia et al., 2020). AD patients present abnormalities of neurovasculature in brain (Singh-Bains et al., 2019), and vascular lesion is frequently associated with some pathological features of AD, such as deposition of amyloid β (Aβ) plaques and neurofibrillary tangles composed of phosphorylated tau (pTau) (Iadecola, 2013), implying a link between AD and VaD. Based on the imaging and pathological changes, VaD is classified into several subtypes, including multi-infarct dementia, small vessel dementia, strategic infarct dementia, hypoperfusion dementia, hemorrhagic dementia, hereditary vascular dementia, and AD with cardiovascular disease (O'Brien and Thomas, 2015).

The pathogenesis of VaD has been described as a multifactorial process, resulting in neuronal injury and related cognitive deficits. Vascular pathology, such as blood-brain barrier (BBB) impairment, is common in dementias, and is related with cognitive decline (Bowman et al., 2018; Skillback et al., 2017). White matter is particularly vulnerable to small vessel disease and white matter lesion with myelin loss represents a hallmark of VaD (Ihara et al., 2010). White matter consists mostly of nerve fibers (axons) and glial cells, including microglia, astrocytes, oligodendrocytes and pericytes (Hase et al., 2018). Chronic cerebral hypoperfusion triggers glia cell activation preferentially in white matter (Wakita et al., 1994), which could be a cause of neuronal damage and white matter degeneration, leading to cognitive impairment in dementia (Hase et al., 2018).

Microglia play dual roles in modulating inflammatory responses upon pathophysiological changes. Microglia adopt resting and activated states. The transition between resting and activated states correlates with the morphological changes from ramified to ameboid features. There are two phenotypes of activated microglia, namely the classically activated pro-inflammatory M1 and the alternatively activated anti-inflammatory M2 phenotypes (Orihuela et al., 2016).

Spatiotemporal dynamics of microglia are involved in BBB leakage and vascular remodeling following injury. Increased BBB permeability, reflected by Evans blue dye or albumin leakage, leads to the focal activation of microglia (Ju et al., 2018; Nimmerjahn et al., 2005). During early phase of vascular injury, chemokines generated by endothelial

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cells attract microglia to the vessels, and these juxtavascular microglia play a beneficial function in the maintenance of BBB integrity (Haruwaka et al., 2019). However, sustained inflammation drives the transition of microglia from a protective to a detrimental phenotype. The activation of harmful microglia augments BBB disruption by generating pro-inflammatory cytokines and phagocytosing astrocytic end-feet and axons. In this review, we focus on the functional role of microglia in the pathogenesis of VaD, with an emphasis on cellular and molecular mechanisms involved in these processes.

2. Models of VaD

Several genetic models have emerged for understanding this disorder. For instance, spontaneously hypertensive/stroke prone rat, transgenic mouse models of type 2 diabetic mellitus, cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (for details, see Tuo et al., 2021). Taking into account that a transgenic animal usually has genetically altered trait that mimics certain genetic risk factor, but could not reflect all aspects of VaD, investigators have now utilized surgical models, especially the vessel occlusion or stenosis in rodents as well as non-human primates, for study. In vitro model has also been established by exposing cells to lipopolysaccharide (LPS) challenge or oxygen-glucose deprivation (OGD).

2.1. Vessel occlusion/stenosis models of VaD

2.1.1. Rat model

Based on literatures, rat two-vessel occlusion (2-VO), also known as bilateral common carotid artery occlusion (BCCAo), model was most widely used to mimic chronic global hypoperfusion in vivo (Fig. 1). To avoid the influences of estrogen on results, male Sprague Dawley (SD) or Wistar rats are commonly applied in this model (Bramlett, 2005). In this model, bilateral carotid arteries were separated from vagus nerve and then occluded with 4–0 silk sutures permanently (Farkas et al., 2004; Zhao et al., 2021b). With an attempt to ameliorate animal mortality rate, some research groups ligate the bilateral carotid arteries sequencely with one-week interval (Liu et al., 2020). This model leads to the white matter lesion, predominantly in the hippocampus and corpus callosum,

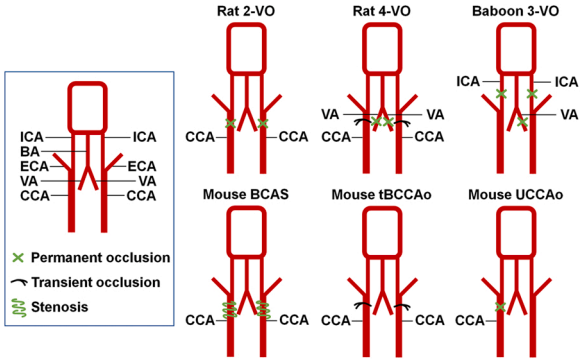

Fig. 1. Schematic drawing of vessel occlusion/stenosis models of VaD. Rat 2-VO, 4-VO, baboon 3-VO, mouse BCAS, tBCCAo, UCCAo models were presented. 2-VO, 2-vessel occlusion; 3-VO, 3-vessel occlusion; 4-VO, 4-vessel occlusion; BA, basilar artery; BCAS, bilateral carotid artery stenosis; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; tBCCAo, transient bilateral common carotid artery occlusion; UCCAo, unilateral common carotid artery occlusion; VA, vertebral artery. Illustrations of vessel occlusion techniques were drawn based on the schematic representations or descriptions in Slakter et al. (1984) (rat 2-VO), Pulsinelli and Brierley (1979) (rat 4-VO), Washida et al. (2019) (baboon 3-VO), Shibata et al. (2004) (mouse BCAS), Zhen and Dore (2007) (mouse tBCCAo), and Yoshizaki et al. (2008) (mouse UCCAo). Different strains of animals may show considerable anatomical variations in the vessel architecture.

resulting in the impairment of cognitive performance. 2-VO model was not suitable for mice because of their incomplete cerebral circle of Willis and may die due to enhanced susceptibility to global cerebral ischemia (Fujii et al., 1997). Another limitation of this model is the rapid reduction of cerebral blood flow following surgery.

In some studies, four-vessel occlusion (4-VO) model was employed in rat to achieve transient global hypoperfusion (Nagata et al., 2019; Rishitha and Muthuraman, 2020). In this model, vertebral arteries are permanently occluded and carotid arteries are usually transiently occluded (Pulsinelli and Brierley, 1979) (Fig. 1). Surgeries are conducted on consecutive days.

2.1.2. Mouse model

Many laboratories utilize the bilateral carotid artery stenosis (BCAS) model to induce chronic cerebral hypoperfusion in mouse. In this assay, microcoils with an internal diameter of 0.18 mm were attached bilaterally to the carotid arteries to narrow the arteries and thereby reduce the blood supply (Shibata et al., 2004) (Fig. 1). White matter integrity, behavioral and cognitive function is impaired in mice following BCAS (Han et al., 2020; Hase et al., 2017; Manso et al., 2018; Suzuki et al., 2021; Yu et al., 2020). However, the strain is limited to C57BL/6 for this model because other stains may exhibit greatly varied cerebral blood flow following surgery (Tuo et al., 2021).

In addition, transient bilateral common carotid artery occlusion (tBCCAo) model was also utilized in mouse experiments (Zhen and Dore, 2007). In this model, the bilateral common carotid arteries of mice were occluded by silk strings for a period of time duration (e.g. 30–50 min constantly or with intervals), followed by reperfusion (Kim et al., 2017; Siracusa et al., 2017; Wang et al., 2020) (Fig. 1).

Unilateral common carotid artery occlusion (UCCAo), in which either right or left common carotid artery was ligated permanently, with the other artery untouched, was also applied as a model of VaD in mouse (Yoshizaki et al., 2008) (Fig. 1). UCCAo results in cognitive impairment and motor deficits, but does not cause cerebral infarction in mouse (Kim et al., 2017; Ma et al., 2012; Thammisetty et al., 2021).

2.1.3. Gerbil model

In view of the incompletely formed cerebral circle of Willis, bilateral common carotid arteries were occluded for a short time period, generally 5–10 min, by artery clips in gerbils (Chen et al., 2021; Min et al., 2013; Yang et al., 2016).

2.1.4. Non-human primate model

The use of non-human primate as model organism can faithfully simulate the disease phenotype in the patients and may have important translational values. Chronic cerebral hypoperfusion was induced in baboon (*Papio anubis*) using three-vessel occlusion (3-VO), in which bilateral internal carotid arteries and the left vertebral artery were occluded for 28 days (Chen et al., 2016a) (Fig. 1). Severe white matter injury, mainly in the deep white matter, was found at 14 days after surgery.

2.1.5. Model validation

In order to confirm the validity of animal model, Doppler flowmeter is generally applied to monitor the carotid blood flow. Open field, Morris water maze, radial arm maze tests, novel object recognition tests were usually performed for accessing cognitive and behavioral impairments (Table 1). Bederson neurological scoring can be utilized for evaluating neurological deficits (Bederson et al., 1986; Wang et al., 2019b). White matter abnormalities in hypoperfused rodents can be detected using magnetic resonance imaging (MRI) (Holland et al., 2011). Luxol fast blue (LFB) staining, also known as Klüver-Barrera staining, is commonly used to label myelin sheaths because this dye targets the lipoproteins of the myelin sheath. Moreover, the demyelinated lesions of white matter can be reflected by reduced immunoreactivity of myelin basic protein (MBP), a myelin-related protein. Ultrastructural changes in myelinated

Table 1
Assays and observing indexes commonly used for assessing animal models of VaD.

Observing indexes/ Parameters	Assay	References*
Behavioral alterations		
Locomotor activity and anxiety-like behavior	Open field	(Suzuki et al., 2021)
Spatial learning and memory	Morris water maze	(Zhou et al., 2021)
Short-term spatial memory	Elevated pulse maze	(Rishitha and Muthuraman, 2020)
Spatial working memory	Radial arm maze	
	3-arm maze (T maze)	(Liu et al., 2021; Yang et al., 2016)
	8-arm maze	(Coltman et al., 2011; Lee et al., 2021)
	9-arm maze	(Hase et al., 2017)
Learning and memory	Novel object recognition	(Lee et al., 2017; Nimmerjahn et al., 2005; Wakita et al., 1994)
Cognitive disturbance	Passive avoidance	(Shinozaki et al., 2017; Thammisetty et al., 2021)
Cerebral blood flow and vessel formation		
Regional CBF	Doppler flowmeter	(Yang et al., 2016; Yu et al., 2020)
Regional CBF	LSCI	(Liu et al., 2021; Zhao et al., 2021b)
Regional CBF	MRI	(Zhang et al., 2020b)
Red blood cell velocity	Two phone imaging	(Wang et al., 2019a)
Arteriole pulsatility and diameter		
Arterial diameter and cerebral vascular density	SRA	(Zhang et al., 2020b)
Glucose metabolism ^{18}F-FDG	microPET/CT	(Yang et al., 2016)
White matter pathology		
AD, FA, MD, RD	MRI	(Ben-Ari et al., 2019; Holland et al., 2011; Liu et al., 2021; Wang et al., 2019a)
CAP	Electrophysiology	(Manso et al., 2018)
Histology		
HE	Staining	(Coltman et al., 2011;Zhou et al., 2021)
Myelin and axon-glial integrity		
LFB	Staining	(Ma et al., 2015)
MBP	Immunostaining, WB	(Coltman et al., 2011; Holland et al., 2011; Ma et al., 2015; Wang et al., 2019a)
MAG	Immunostaining, WB	(Coltman et al., 2011; Manso et al., 2018; Sigfridsson et al., 2020; Wang et al., 2019a)
NF	Immunostaining	(Wang et al., 2019a)
Caspr (paranodes) and $Na_{v1.6}$ (Node of Ranvier)	Immunostaining	(Manso et al., 2018; Wang et al., 2019a)
Ultrastructure	TEM	(Ma et al., 2015; Suzuki et al., 2021)
Neuronal density		
Nissl	Staining	(Chen et al., 2021; Yu et al., 2020)
NeuN	Immunostaining	(Bederson et al., 1986; Han et al., 2020; Suzuki et al., 2021)
Synaptic plasticity		
LTP	Electrophysiology	(Han et al., 2020)
BBB permeability		
IgG	Immunostaining	(Sigfridsson et al., 2020)
Evans blue	Staining	(Roberts et al., 2018)
Fibrinogen	Immunostaining	(Chen et al., 2016a)

Note: ^{18}F-FDG: ^{18}F-fludeoxyglucose; AD: axial diffusivity; BBB: blood-brain barrier; CAP: compound action potential; CBF: cerebral blood flow; FA: fractional anisotropy; HE: hematoxylin and eosin; IgG: immunoglobulin G; LFB: Luxol fast blue; LSCI: laser speckle contrast imaging; LTP: long-term potentiation; MAG: myelin-associated glycoprotein; MBP: myelin basic protein; MD: mean diffusivity; MRI: magnetic resonance imaging; NF: neurofilament; PET/CT: positron emission tomography/computed tomography; RD: radial diffusivity; SRA: synchrotron radiation angiography; TEM: transmission electron microscopy. *Representative reference.

axons can also be examined under electron microscopy.

2.2. Values of animal models for the study of VaD pathogenesis

Although none of the animal or cell model is capable of manifesting the actual situation of VaD in human, application of these models has enhanced the understanding of the pathogenic mechanism of VaD. Vessel occlusion mentioned above results in global cerebral hypoperfusion, followed by white matter injury, learning and memory deficits in animals, replicating the key pathogenic features of VaD (Jiwa et al., 2010). Middle cerebral artery occlusion (MCAo), leading to focal cerebral hypoperfusion in rodents, is generally used to mimic cerebral ischemia but also causes neurological damage as well as impairments in learning and memory (Jiwa et al., 2010). Notably, increased inflammation has been detected in pathologic brains from various animal models of VaD (Venkat et al., 2015). LPS, the endotoxin within bacterial cell wall, causes inflammation and BBB disruption in rodents (Banks et al., 2015). Therefore, LPS injection is frequently used in rodent models to generate an inflammatory status in brain. Increased number of inflammatory cells has been noted in the pathological condition of aging and age-related disorders (Liu, 2017). Among these cells, microglia are the principle players in neuroinflammation. Abnormal activation of microglia has been universally detected in different models of VaD. The functional roles of activated microglia in VaD pathology will be discussed in the following sections.

2.3. In vitro cell models

The neurovascular unit (NVU) encompasses neurons, glia (microglia, astrocytes and oligodendrocytes) and vascular cells (endothelial cells, pericytes and vascular smooth muscle cells) together with extracellular matrix components (Kisler et al., 2017). As a complement to animal model of VaD, several studies employed a cell model through exposing cultured NVU cells to OGD (Li et al., 2012; Wang et al., 2012). In this model, cells incubated with glucose-free medium were placed in a hypoxia chamber, a condition mimicking hypoxia caused by the reductions of cerebral blood flow in VaD (Raz et al., 2016).

Dysregulation of neuroinflammation in white matter is the critical feature of neuropathology in dementia (Raz et al., 2016), and this phenotype can be mimicked by exposing cultured cells (e.g. microglia) to infectious stimuli, such as LPS (Gargouri et al., 2018; Kim et al., 2017). Being a ligand, LPS elicits inflammatory responses of microglia through binding to and activating receptors such as Toll-like receptor 4 (TLR4) and CD14 (Kawai and Akira, 2007). The cross-talk between the individual cell types of the NVU can be studied by treatment with conditioned medium or using co-culture system.

3. Altered expression of microglial biomarkers in VaD

Upon stimuli, microglia undergo morphological changes and express different biomarkers. Although there a variety of biomarkers used to label microglia, changes in ionized calcium binding adapter molecule 1 (Iba1), cluster of differentiation 11b (CD11b), CD68 and triggering receptor expressed on myeloid cells 2 (TREM2), have been documented in experimental models of VaD by numerous laboratories. Hence, we here focus on discussing the altered expressions of these markers in VaD pathology.

3.1. Iba1 and CD11b

Iba1 and CD11b label both activated and resting microglia (Lee et al., 2002; Nikolakopoulou et al., 2013). Iba1 facilitates microglial migration

and phagocytosis via modulating actin reorganization (Ohsawa et al., 2004). Although the cytoplasm expression of Iba1 can be detected in both resting and activated microglia, increased Iba1 immunoreactivity together with an ameboid change in morphology is considered as a feature for activated microglia. In cerebral cortex derived from subjects ≥ 65 years old, microglia with abundant short processes, were labeled with Iba1 (Fahrenhold et al., 2018). In rat 2-VO model, increased number of Iba1-positive microglia was detected in the cerebral cortex as well as hippocampus region (Lee et al., 2021, 2015; Liu et al., 2020; Zhao et al., 2021b). Similarly, sustained enhancement of Iba1 expression was found in the brain of mouse UCCAo and BCAS models (Ben-Ari et al., 2019; Han et al., 2020; Hase et al., 2017; Ma et al., 2012; Manso et al., 2018; Thammisetty et al., 2021). Single dose of LPS injection led to a progressive increase of Iba1-positive microglia in the hippocampus and parietal cortex of mice (Bowyer et al., 2020). Mice deficient in nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor, exhibited higher baseline level of microglia in brain (Rojo et al., 2010). Absence of Nrf2 further exacerbated the density of Iba1-positive cells and white matter damage in mice subjected to chronic cerebral hypoperfusion (Sigfridsson et al., 2020).

CD11b is another reliable marker for microglia. Increased level of CD11b was found in rats subjected to 2-VO (Miyamoto et al., 2001) and also in LPS-treated BV2 cells (Zhang et al., 2021a).

3.2. CD68

CD68, a macrophage-specific protein, is mainly expressed in the lysosomal membrane of microglia (Hendrickx et al., 2017). The expression of CD68 is elevated in ameboid microglia and therefore phagocytic microglia can be identified by CD68 (Wong et al., 2005). Marked activation of CD68-positive microglia was observed three days following cerebral hypoperfusion in baboons subjected to 3-VO (Washida et al., 2019). In the cerebral white matter areas of patients with small vessel disease, activated Iba1-positive microglia and CD68-positive macrophages were observed, which may contribute to the removal of damaged vessels (Forsberg et al., 2018). However, Matsumoto et al. revealed that antibodies to CD11b-, CD68-, and isolectin B4-labeled neutrophils, rather than microglia, deposited in the lesion core of rat brain following transient MCAo (Matsumoto et al., 2007).

3.3. TREM2

Serving as a receptor that locates on the surface of microglia, TREM2 mediates microglial metabolism in response to lesion (Nugent et al., 2020; Ulland et al., 2017). It is recognized as a biomarker for activated and phagocytic, rather than resting microglia. The expression of cerebral TREM2 was upregulated in diabetic rats subjected to VaD (2-VO) (Zheng et al., 2021), and also in mice subjected to tBCCAo injury (Wang et al., 2020). Similar results were obtained in cultured cells, as elevated TREM2 was detected in BV2 microglia cells exposed to high glucose and hypoxia (Zheng et al., 2021). Silencing of TREM2 promoted the production of pro-inflammatory cytokines from BV2 cells after high glucose and hypoxia treatment, whereas overexpressing TREM2 suppressed the release of these cytokines, suggesting TREM2 may negatively modulate inflammatory response (Zhang et al., 2020a). Overexpression of TREM2 in brain efficiently inhibited microglial activation by promoting microglia polarization from M1 towards M2 phenotype, prevented the cognitive deficits and alleviated neuronal loss in hippocampus of VaD mouse following tBCCAo, indicating TREM2 may play a protective role through modifying microglial phenotype (Wang et al., 2020).

Interestingly, in the brain samples of subjects aged over 65 years, Iba1-positive microglia did not express TREM2. The immunoreactivity of TREM2 was detected in intravascular monocytes (Fahrenhold et al., 2018). In cerebral sections of subjects with acute infarcts (1–3 days), several extravascular parenchymal cells within the acutely infarcted zone were found to be TREM2 positive, implicating the TREM2-positive intravascular monocytes might be recruited from the bloodstream into brain parenchyma in response to infarct. Therefore, results should be interpreted with particular caution, given that some markers, such as TREM2, may not be exclusively expressed by microglia.

Considering the shared lineage of microglia with infiltrating immune cells, biomarkers can be common between microglia and other types of cells (Hopperton et al., 2018). Therefore, selection of appropriate biomarker, combined with morphological examinations, is required for identifying activated microglia.

4. Diverse functions of microglia in VaD pathology

4.1. Microglial chemotaxis

4.1.1. Chemoattractants guide the motility of microglia

Microglial chemotaxis, referred to the migratory capability of microglia to spatial locations, is an early response to vascular injury. A variety of chemoattractants guide the directional movement of microglia. In rodent and human, cerebral white matter contains higher amount of chemokines, such as C-C chemokine ligand (CCL) 2 and CCL3 compared to gray matter, which guide the migration of cultured microglia (Zhang et al., 2021b). The cell type-specific release and response of chemokine has also been addressed by several studies. For instance, endothelial cells release CCL5, which attracts microglia to the vessels via binding to its receptor CCR5, in response to acute inflammatory stimuli (Haruwaka et al., 2019) (Fig. 2). Moreover, chemokine C-X3-C motif ligand 1 (CX3CL1, also known as fractalkine), mainly expressed by neurons, is released following inflammatory stimuli (Cotter et al., 2002). Under pathological insults, the secretion of CX3CL1 is elevated, eliciting the movement of microglia towards the site of injury or inflammation by binding to CX3CL1 receptor in microglia (Cotter et al., 2002) (Fig. 2). The expressions of both CX3CL1 and CX3CR1 were increased in the hippocampus of 2-VO rats (Mao et al., 2020). Inhibition of the release of CX3CL1 from neurons may suppress the M1 polarization of microglia (Mao et al., 2020).

4.1.2. ATP guides the motility of microglia

Astrocytes are able to release nucleotides, such as adenosine 5'-

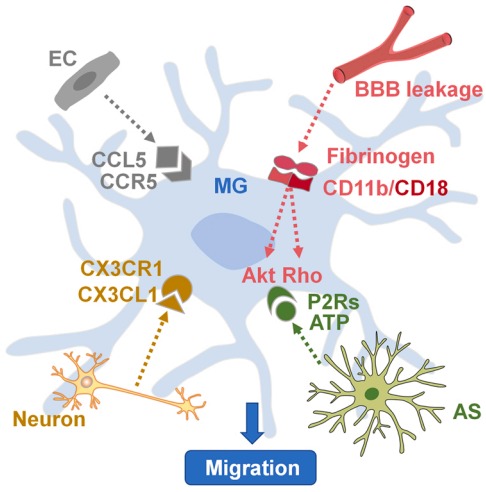

Fig. 2. Schematic drawing of microglial chemotaxis under the pathology of cerebral hypoperfusion. Chemoattractants and ATP, released from endothelial cells, neurons and astrocytes, guide the motility of microglia by binding to their specific receptors. Increased permeability of BBB leads to the leakage of fibrinogen, which exacerbates microglial migration by binding to microglial receptor and activating Akt and Rho signaling. AS, astrocytes; ATP, adenosine 5'-triphosphate; BBB, blood-brain barrier; CCL5, C-C chemokine ligand 5; CCR5, CCL5 receptor; CX3CL1, C-X3-C motif ligand 1; CX3CR1, CX3CL1 receptor; EC, endothelial cells; MG, microglia; P2Rs, P2 purinoceptors.

triphosphate (ATP). Being a potent agonist for purinergic receptors, ATP evokes a rapid chemotactic microglial response towards brain injury through binding to P2 purinoceptors (P2Rs) and activating microglia (Davalos et al., 2005; Honda et al., 2001) (Fig. 2). P2Rs include ionotropic P2XRs and metabotropic P2YRs. Current study emphasizes on the importance of P2YR12, a subtype of G-protein coupled P2YR, in modulating the chemotaxis of microglia following acute vascular injury (Lou et al., 2016). Microglia in P2YR12-deficient mice exhibited abolished directional branch outgrowth towards nucleotides as well as sites of cortical injury (Haynes et al., 2006). In addition, deficiency of TREM2 also impairs the extension of microglia towards cerebral injury site (Mazaheri et al., 2017).

4.1.3. *BBB leakage exacerbates microglial migration and activation*

The increased permeability of BBB leads to the leakage of plasma proteins, including fibrinogen or immunoglobulin G (IgG), from bloodstream into the brain parenchyma. The leaked proteins, such as fibrinogen, serve as environmental cues that drive the mobility and status transformation of microglia. Basal lamina damage and BBB opening, accompanied with enhanced microglial activation and pericyte detachment, was observed in inflamed brain of LPS-treated mice (Nishioku et al., 2009).

Data from postmortem AD patients unravel an extensive diffuse deposition of fibrinogen, indicative of BBB leakiness, is associated with microglia in brain tissues (Ryu and McLarnon, 2009). Fibrinogen results in dendritic spine elimination and cognitive defects in transgenic mouse model of AD (Merlini et al., 2019). High plasma level of fibrinogen correlates with increased risks of both AD and VaD (van Oijen et al., 2005). In accordance with this finding, histological study reveals that increased extent of fibrinogen labeling in histopathological lesion of white matter, that is defined by CD68-positive staining, is related to the increased risks of dementia (Hainsworth et al., 2017). Injection of fibrinogen solution into the cortex of mouse resulted in rapid and persistent microglial responses (Davalos et al., 2012). It contributes to the clustering of microglia surrounding the vasculature and releasing of ROS. It also promotes the migration ability of cultured microglial BV2 cells (Jolivel et al., 2015). Microglia CD11b/CD18 is a heterodimer consisting of an α-subunit (CD11b) and a β-subunit (CD18). Acting as a ligand, fibrinogen binds to the integrin receptor CD11b/CD18 and provokes downstream Akt and Rho signaling, thereby activating microglia (Adams et al., 2007) (Fig. 2). Pharmacological blockage of fibrin formation or genetic interference of fibrinogen binding motif ameliorated microglial clustering and axon injury (Davalos et al., 2012).

4.2. *Microglia-mediated inflammatory responses*

4.2.1. *Anti-inflammatory function*

The secretory property of microglia has been well characterized. Microglia are capable to release both anti- and pro-inflammatory cytokines depending on its status (Fig. 3). Upon stimulation with interleukin (IL)− 4/IL-13 or IL-10 signals, microglia can switch to an M2 phenotype. In this status, microglia upregulate the expression of receptors (e.g. CD206, CD163), cytosolic enzymes (e.g. arginase-1), secretory proteins (e.g. YM1), and secret anti-inflammatory cytokines (e.g. IL-4, IL-10, transforming growth factor [TGF]-β), which facilitate tissue repair and resolution of inflammation (Lan et al., 2017; Orihuela et al., 2016). Note worthily, the anti-inflammatory cytokines counteract pro-inflammatory cytokines. Despite microglia generate anti-inflammatory cytokine TGF-β and pro-inflammatory cytokine tumor necrosis factor (TNF)-α simultaneously, sustained TGF-β but a transient TNF-α secretion was detected in phagocytic microglia (Ryu et al., 2012). Such secretion pattern can be reversed by LPS challenge. A likely explanation for the beneficial or detrimental role of microglia might be dependent on the concentration, release duration, and dominant position of cytokines.

Compared to other cells of the NVU (microglia, astrocytes, and pericytes), brain endothelial cells were more susceptible to death in response to OGD (Redzic et al., 2015). Anti-inflammatory cytokines, such as TGF-β1 and IL-6, from microglia-conditioned medium mitigated OGD-induced damage in brain endothelial cells. Microglia protect against astrocyte death following OGD possibly by secreting TGF-β1 (Redzic et al., 2015).

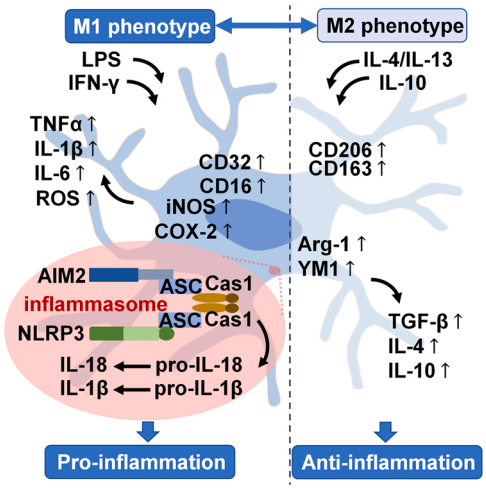

Fig. 3. Microglia-mediated inflammatory responses under the pathology of cerebral hypoperfusion. Microglia can experience M1 and M2 polarization upon different stimuli. LPS or IFN-γ upregulates the expressions of CD32 and CD16, elevates the production of pro-inflammatory cytokines, ROS, iNOS, COX, and triggers the presence of inflammasome (in red circle), and thus microglia play a pro-inflammatory function. NLRP3 and AIM2 inflammasomes result in the catalytic cleavage of pro-IL-1β and pro-IL-18 into their mature forms. Upon stimulation with IL-4/IL-13 or IL-10, microglia switch into an M2 phenotype and facilitate tissue repair. In this status, CD206, CD163, Arg-1, YM1, and anti-inflammatory cytokines were upregulated. AIM2, absent in melanoma 2; Arg-1, arginase-1; ASC, apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain; Cas1, Caspase 1; COX-2, cyclooxygenase-2; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

4.2.2. *Pro-inflammatory function*

Chronic hypoperfusion shifted microglial polarization from M2 to M1 in rat, accompanied with the increased expression of M1 phenotype markers and the decreased generation of M2 phenotype markers (Xu et al., 2021). Activated microglia exhibit the retraction of their processes and the adoption of a characteristic ameboid morphology. M1 microglia fuel the inflammatory process and accelerate neuronal death via expressing immunoglobulin Fc receptors (e.g. CD16/CD32), releasing pro-inflammatory cytokines (e.g. TNF-α, IL-1β, IL-6), metabolic enzymes (e.g. inducible nitric oxide synthase [iNOS]), nitric oxide (NO), and metabolic byproducts (e.g. reactive oxygen species [ROS]) in response to pathological changes or various stimulants, including LPS and interferon (IFN)-γ (Fig. 3). The level of destructive pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, were increased in rats following chronic hypoperfusion (Hu et al., 2019; Lee et al., 2015; Mao et al., 2020). The generation of enzymes involved in inflammatory responses, such as cyclooxygenase (COX)− 2, is also elevated (Lee et al., 2015). In addition, enhanced oxidative stress, with the presence of enhanced ROS production, increased malondialdehyde (MDA) level and decreased superoxide dismutase (SOD) activity and glutathione expression were also detected in rodent models of VaD (Hu et al., 2019; Ma et al., 2012).

Recent studies highlight the role of nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome and absent in melanoma 2 (AIM2) inflammasome in microglia-mediated maturation of pro-inflammatory cytokines IL-1β and IL-18. NLRP3 inflammasome is composed of NLRP3, the adapter molecule apoptosis-

associated speck-like protein containing a C-terminal caspase recruitment domain (ASC) and pro-caspase 1 (Fig. 3). It is shown that osthole inhibited the NLRP3 expression and microglial activation in rat following chronic hypoperfusion (Liu et al., 2020), implying the involvement of NLRP3 inflammasome in microglial activation. Ferulic acid inhibited NLRP3 expression and IL-1β production by benzo(a) pyrene-treated microglial BV2 cells (Bao et al., 2019). Suppression of NLRP3 inflammasome may be a promising strategy for anti-inflammation therapy (He et al., 2018; Yu et al., 2021). AIM2, an interferon-inducible HIN-200 family member, contains a pyrin domain that interacts with ASC to activate caspase-1 (Fernandes-Alnemri et al., 2009; Hornung et al., 2009). The presence of both NLRP3 and AIM2 inflammasome results in the catalytic cleavage of pro-IL-1β and pro-IL-18 into their mature forms. The generation of IL-1β and IL-18 was elevated in hypoperfused mouse brain (Matsuyama et al., 2020). In addition, chronic cerebral hypoperfusion increased AIM2 inflammasome in microglia from cerebral white matter and corpus callosum of mice and brain autopsies of patients following cerebral infarction (Matsuyama et al., 2020). Knock out of AIM2 or pharmacological inhibition of caspase-1 prevented the cognitive impairment in stroke mice (Kim et al., 2020). However, recent study indicated that AIM2 deficiency in microglia potentiated neuroinflammation and the pathogenesis of experimental autoimmune encephalomyelitis through an inflammasome-independent mechanism (Ma et al., 2021). Therefore, the exact role of AIM2 inflammasome in the VaD pathogenesis still requires further investigation.

4.3. Microglia produce matrix-degrading enzymes

Microglia produce different classes of matrix-degrading enzymes, including matrix metalloproteinases (MMPs), heparanase, and cathepsins (or cysteine proteases) (Lively and Schlichter, 2013) (Fig. 4A).

4.3.1. Matrix metalloproteinases

MMPs are a large family of zinc- and calcium-dependent endopeptidases that participate in the white matter injury of VaD. MMPs result in the opening of BBB through inducing the degradation of tight junction proteins (Yang et al., 2007). Emerging studies reported the increased MMP generation and decreased expression of tight junction proteins, such as zonula occluden-1 (ZO-1), in rodent cerebrum modeling VaD, which consequently induced BBB breakdown.

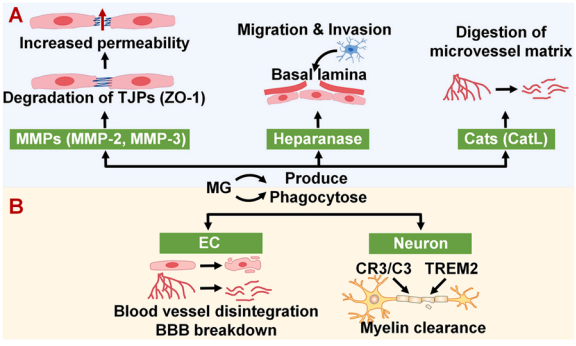

Fig. 4. The production of matrix-degrading enzymes and phagocytosis of microglia under the pathology of cerebral hypoperfusion. (A) Microglia produce matrix-degrading enzymes, including MMPs, heparanase, and cathepsins. MMPs, such as MMP-2 and MMP-3, degrade TJPs and increase the BBB permeability. Heparanase is involved in the migration and invasion of microglia across the basal lamina. Cats, such as CatL, contribute to the digestion of microvessel matrix. (B) Microglia phagocytose EC and myelin, leading to blood vessel disintegration, BBB breakdown, and neuronal damage. BBB, blood-brain barrier; CatL, cathepsin L; Cats, cathepsins; CR3, complement receptor 3; EC, endothelial cell; MG, microglia; MMPs, matrix metalloproteinases; TJPs, tight junction proteins; TREM2, triggering receptor expressed on myeloid cells 2; ZO-1, zonula occluden-1.

Accumulative evidence demonstrates that several subtypes of MMPs are produced by activated juxtavascular microglia in response to stimuli or injury (Konnecke and Bechmann, 2013). For instance, CD68-positive microglia, expressing matrix metalloproteinase 3 (MMP-3, also known as stromelysin-1), were observed surrounding the infarcts in brain tissues derived from patients with VaD (Rosenberg et al., 2001). LPS alone or in combination with phorbol myristate acetate induced MMP-3 expression in cultured microglia (Woo et al., 2008). Expression of MMP-2 was detected in activated microglia of the corpus callosum and optic tract of rat following 2-VO injury (Ihara et al., 2001). Injection of AG3340, a MMP-2 specific inhibitor, attenuated microglial activation, BBB opening and white matter lesion in rats subjected to cerebral hypoperfusion injury (Nakaji et al., 2006). Similar results were obtained in BCAS-treated mice deficient in MMP-2 (Nakaji et al., 2006). Interestingly, transplantation of a human microglia cell line, HMO6, inhibited the microglial activation, decreased the MMP-2 generation in microglia as well as the severity of white matter damage in rats following cerebral hypoperfusion (Narantuya et al., 2010). Similar to MMP-2, MMP-9 is another gelatin-binding MMP. Increased MMP-9 level was found in LPS-treated microglia cultured in vitro (Liuzzi et al., 2004). Although upregulated protein expression of MMP-9 was observed in cortex of rat after cerebral hypoperfusion (Lee et al., 2017; Song et al., 2020), no MMP-9 was found in microglia (Ihara et al., 2001). Incubation with ROS inhibitors, such as diphenylene iodonium or N-acetyl-cysteine, remarkably decreased the levels of MMP-1, − 3 and − 9 in cultured microglia exposed to LPS (Woo et al., 2008). In addition, treatment of cells with MMP-3 or MMP-9 inhibitor also alleviated the ROS production by microglia (Woo et al., 2008). In keeping with this observation, increased mRNA levels of MMP-2 and MMP-3 were detected in LPS-injected brain, especially in the perivascular cells surrounding the injection site, prior to the induction of cytokines such as TNF-α (Mun--Bryce et al., 2002). These observations raise concerns that the generated MMPs by microglia can reciprocally activate microglia and aggravate inflammatory responses.

4.3.2. Heparanase

Cultured microglia express the extracellular matrix-degrading enzyme heparanase, the expression of which is increased upon LPS challenge (Takahashi et al., 2008). Heparanase is suggested to be involved in the migration and invasion of microglia across the basal lamina surrounding cerebral vasculature, as pharmacological inhibition of heparanase activity greatly blocked the migratory and invasive capacity of microglia across the Matrigel-coated pored membrane (Takahashi et al., 2008).

4.3.3. Cathepsins

The human lysosomal cysteine proteases include cathepsins B, C, F, H, K, L, O, S, V, W, and X. The generation and activities of cathepsin B were potentiated in glial cells in the cerebral cortex and subcortical white matter of stroke-prone spontaneously hypertensive rats (Chue et al., 1993). Increased activity of cathepsin L, but not cathepsin B, was observed in the ischemic core of non-human primate MCAo model (Gu et al., 2015). Using OGD model, the non-neuronal source of cathepsin L was examined in primary endothelial cells, microglia and astrocytes. An obvious increase of cathepsin L activity was found in microglia cultured on matrix substrates, in comparison with other cell types under OGD (Gu et al., 2015). Moreover, cathepsin L released from microglia led to the digestion of microvessel matrix (Gu et al., 2015). Cathepsin C stimulated the production of chemokines including chemokine (C-C motif) ligand 2 (CCL2) and chemokine (C-X-C motif) ligand 2 (CXCL2) from cultured microglia cells (Zhao et al., 2021a). Absence of cathepsin K aggravated microglial activation and BBB breakdown in mice after focal cerebral ischemia (Zhao et al., 2019).

4.4. Microglial phagocytosis

Microglial phagocytic response contributes to the refinement of central nervous system during development, primarily via eliminating surplus synapses and pruning myelin sheaths (Hughes and Appel, 2020). Ablation of microglia in mature brain impairs structural plasticity in synapses and results in learning and memory deficits in mice (Parkhurst et al., 2013). Microglial phagocytosis also functions in pathological conditions. For instance, juxtavascular microglia facilitate the temporarily resealing of BBB and benefit the maintenance of BBB integrity during early phase of vascular injury. Activated microglia may contribute to the remodeling of vessels by sequestering the damaged vessels (Forsberg et al., 2018). The transformation of protective microglia into a phagocytic phenotype occurred after sustained inflammation (Haruwaka et al., 2019). Perivascular microglia lead to blood vessel disintegration and resultant BBB breakdown by phagocytosing the endothelial cells in the ischemic penumbra (Jolivel et al., 2015) (Fig. 4B). To support this notion, in the cerebral white matter areas of patients with small vessel disease, activated Iba1-positive microglia and CD68-positive macrophages were observed, which may contribute to the removal of damaged vessels (Forsberg et al., 2018).

Dying neurons send “eat-me” signals which govern the microglial phagocytosis of neuronal debris (Noda et al., 2011). In the striatum of rats subjected to chronic cerebral hypoperfusion, microglia displayed a tendency to adhere to and phagocytose myelin (Zhang et al., 2020b). Complement component C3 and complement receptor 3 (CR3) play crucial roles in mediating microglial phagocytosis. Ablation of the microglial C3a receptor preserved the myelin level and rescued axon in rodents after hypoperfusion (Zhang et al., 2020b). In addition to CR3/C3, TREM2 may also contribute to the modulation of myelin clearance by microglia. Microglia deficient of TREM2 showed impaired phagocytic ability of apoptotic neurons (Takahashi et al., 2005). Consistently, TREM2 deficiency resulted in dysfunctional removal of myelin debris in a mouse model which demyelination occurs secondary to oligodendrocyte death (Poliani et al., 2015), while activation of TREM2 accelerated the elimination of myelin debris and promoted remyelination (Cignarella et al., 2020). Nonetheless, the precise role and underlying mechanism of TREM2-dominated myelin removal in the pathogenesis of VaD still requires to be further confirmed.

Engulfment of dying neurons or debris is believed to be limited to brain immune cells, such as microglia. Interestingly, reactive astrocytes possess a phagocytic feature, that is spatiotemporally different from microglial phagocytosis, following transient ischemic injury (Morizawa et al., 2017). Microglia-mediated phagocytosis occurs at the ischemic core during the early stage, while astrocytic phagocytosis appeared within the ischemic penumbra during the late onset stage (Morizawa et al., 2017).

5. Multicellular crosstalk

Abundant evidence indicates that microglia associate with other NVU cells, such as cerebral endothelial cells, astrocytes, pericytes, etc. through biophysical (direct cell-cell interaction) or biochemical (specific extracellular signals) communication (Fig. 5). Such multicellular crosstalk contributes to the neurovascular pathology and remodeling following hypoperfusion.

5.1. Cerebral endothelial cells

Migrated microglia build physical contacts with endothelial cells by expressing claudin-5, a key mediator for tight junction, and thus contribute to the maintenance of BBB integrity during early stage of inflammation (Haruwaka et al., 2019) (Fig. 5A). CD31, also known as platelet/endothelial cell adhesion molecule 1 (PECAM1), is commonly used to label cerebral vascular endothelial cells and vasculature. LPS challenge induced microglial activation surrounding the

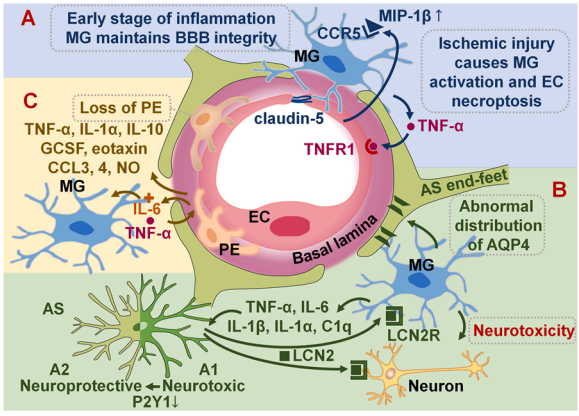

Fig. 5. Proposed schematic diagram of the association between microglia and other neurovascular unit cells under the pathogenesis of VaD. The cross-section of blood-brain barrier shows endothelium, basal lamina, astrocytic end-feet, microglia and pericytes. (A) During early stage of inflammation, microglia contact with endothelial cells by expressing claudin-5, which benefits the maintenance of BBB integrity. Ischemic injury causes TNF-α releasing from microglia and results in endothelial necroptosis. In turn, endothelial cells produce MIP-1β, which affects microglia proliferation by binding to CCR5. (B) Activated microglia disturb the normal distribution of AQP4 in the end-feet of astrocyte and induces astrocyte reaction by generating cytokines. The reactive astrocyte is categorized into A1 (neurotoxic) and A2 (neuroprotective) phenotypes. Microglia switch the A1 to A2 phenotype by decreasing astrocytic P2Y1 receptors. A1 AS can induce neurotoxicity directly and indirectly via releasing LCN2. (C) Pericyte loss occurs under pathology. Pericytes produce cytokines, chemokines and NO. TNF-α triggers the release of IL-6 from pericytes, resulting in microglial activation. AQP4, aquaporin 4; AS, astrocyte; BBB, blood-brain barrier; C1q, complement 1q; CCL, C-C chemokine ligand; CCR5, C-C chemokine ligand receptor 5; EC, endothelial cell; GCSF, granulocyte-colony stimulating factor; IL, interleukin; LCN2, lipocalin-2; LCN2R, LCN2 receptor; MG, microglia; MIP-1β, macrophage inflammatory protein-1β; NO, nitric oxide; PE, pericyte; TNF-α, tumor necrosis factor-α; TNFR1, TNF receptor 1.

CD31-immunolabeled vasculature, accompanied with an obvious loss in astrocytic contact with vasculature, in cerebral tissues of mice (Bowyer et al., 2020). Loss of microglial TREM2 in mouse resulted in the dyscoordination of endothelial cells, linking the microglia-based immune responses with vascular homeostasis (Carbajosa et al., 2018). Administration with exenatide, a glucagon-like peptide-1 receptor agonist, restored the transcriptomic changes in endothelial cells and microglia of aged mouse brain, and mitigated BBB disruption (Zhao et al., 2020). Ischemic injury induced an accumulation of activated microglia with endothelial cells at the ischemic border zone (Chen et al., 2019). These microglia released TNF-α, which bound to its receptor TNFR1 on endothelial cells and caused endothelial necroptosis (Chen et al., 2019).

In turn, endothelial cells modulate the activity of microglia under pathophysiological conditions. Macrophage inflammatory protein-1β (MIP-1β) is a pro-inflammatory cytokine which enhances the viability, proliferation and motility of microglia. Mechanically, the brain microvascular endothelial cells (BMECs)-conditioned medium downregulated the expression of CCR5, a MIP-1β specific receptor, in microglia exposed to MIP-1β (Wang et al., 2011). In addition, phosphorylation of JNK and p38 was also attenuated in MIP-1β-treated microglia cultured with BMECs-conditioned medium. Barely any MIP-1β could be detected in normal BMECs or culture medium from BMECs, whereas OGD-treated BMECs release abundant MIP-1β (Wang et al., 2011). OGD induced injury in cultivated BMECs, which consequently resulted in the increase in the number of microglia (Wang et al., 2012). Inhibition of endothelial cell injury efficiently ameliorated the microglial proliferation (Wang et al., 2012). Taken together, these results suggest that normal endothelial cells play a role in suppression of microglia. However, damaged endothelial cells may exacerbate microglia viability.

5.2. Astrocytes

Astrocytes expand long processes and interact with the endothelium of cerebral capillaries with their end-feet (Fig. 5B). The water channel protein aquaporin 4 (AQP4), concentrated in the astrocytic end-feet, is responsible for the maintenance of water homeostasis. However, in hypoperfused mice, abnormal distribution of AQP4, accompanied with enhanced activation of microglia, was detected (Hase et al., 2018). It should be noted that microglial activation and neuroinflammation precedes astrocytic changes and cerebrovascular pathology (Sudduth et al., 2017), implying microglia-mediated neuroinflammation may be a cause for astrocytic injury.

Interactions between microglia and astrocytes are depicted in cell and animal experiments. Cytokines appear to be pivotal mediators for the communication between microglia and astrocytes. Activated microglia result in astrocyte reaction by producing TNF-α, IL-6, IL-1β, IL-1α and complement 1q (C1q) (Liddelow et al., 2017; Shinozaki et al., 2017). Glial fibrillary acidic protein (GFAP) is a reactive astrocyte marker. Similar to that of M1/M2 microglial phenotype, the reactive astrocytes are categorized into A1 (neurotoxic) and A2 (neuroprotective) phenotypes (Escartin et al., 2021). The A1 reactive astrocytes can be toxic to neurons. Under hypoperfusion condition, lipocalin-2 (LCN2), secreted from reactive astrocytes, binds to its receptor LCN2R on both microglia and hippocampal neurons, and thereby exert both indirect and direct neurotoxicity (Kim et al., 2017). Mice lacking microglia (colony stimulating factor-1 receptor-deficient mice (Ginhoux et al., 2010)) failed to generate neurotoxic astrocytes in response to LPS challenge (Liddelow et al., 2017). It is worth mentioning that microglia can also shift astrocytes into a neuro-supportive phenotype by downregulating astrocytic P2Y1 receptors (Shinozaki et al., 2017).

5.3. Pericytes

Pericytes are vascular mural cells that wrap around endothelial cells in the brain capillaries. Pericyte deficient mice presented abnormalities in white matter structure and function, whereas showing no changes in the number of microglia or astrocytes in white matter (Montagne et al., 2018). Pericytes constrict capillaries and then die in rigor as a result of OGD injury (Hall et al., 2014). Platelet-derived growth factor receptor-β (PDGFRβ) and collagen 4 are commonly used markers for labeling pericytes. The number of collagen 4-positive pericytes was greatly reduced in the frontal white matter of post-mortem brains derived from patients with different dementias, including VaD, post-stroke dementia, AD, and AD-VaD mixed, when compared to post-stroke non-demented stroke survivors and normal aging controls (Ding et al., 2020). Likewise, loss of pericytes and disintegration of microvessels were found in the hippocampus of VaD rat (Lee et al., 2021). The cerebral perivascular pericytes showed characteristics of multipotent stem cells and had the potential to differentiate into functional, phagocytic microglia following ischemia (Sakuma et al., 2016).

Cultured brain microvascular pericytes produce cytokines (pro-inflammatory cytokines, e.g. TNF-α, IL-1α; anti-inflammatory cytokines, IL-10), chemokines (e.g. granulocyte-colony stimulating factor, eotaxin, CCL3, CCL4) and NO in response to LPS (Kovac et al., 2011) (Fig. 5C). Pericyte-conditioned medium protects against the death of microglia and cerebral endothelial cells following OGD (Redzic et al., 2015). TNF-α stimulated the release of IL-6 from cultured pericytes, which provoked the activation of BV2 microglia (Matsumoto et al., 2018; Matsumoto et al., 2014).

It should be noted that microglia may communicate with other types of cells, such as oligodendrocytes and peripheral immune cells. Nevertheless, the cross-talk between microglia and other cells in NVU is not discussed here due to the lack of adequate literatures.

6. Potential therapeutic strategies targeting microglia-modulated neuroinflammation

Although some of the AD medications have also shown modest effects for VaD patients (e.g. donepezil for VaD [ClinicalTrials.gov Identifier: NCT00165737] (Roman et al., 2010) and galantamine for VaD [NCT00035191] and mixed dementia [AD/VaD, NCT00261573] (Erkinjuntti et al., 2002)), the efficacious approved pharmacological therapy available for VaD is still lacking (Farooq et al., 2017). Therapeutic options that targeting microglia-mediated neuroinflammation are of benefit to studied animals, but require to be explored in more depth in clinical trials.

6.1. Inhibition of microgliosis

A robust and sustained increase in the number of microglia, also known as microgliosis, is a predominant feature in hypoperfused rodent brain (Coltman et al., 2011; Manso et al., 2018). Enhanced microglia proliferation is accompanied with the disturbance in axon-glial integrity. Pharmacological inhibition of microglial activation can be achieved by the use of minocycline, a tetracycline antibiotic, which dampens the microglial proliferation and the consequent production of IL-1β and NO (Tikka et al., 2001). Minocycline decreased the generation of superoxide from cultured microglia in response to OGD (Yenari et al., 2006). In hypoperfused rodents, minocycline yielded protective effects against BBB disruption, inflammation, oxidative stress, structural and functional alterations of white matter, and cognitive impairment (Cai et al., 2008; Cho et al., 2006; Manso et al., 2018; Yang et al., 2018). A study group further emphasized the importance of early therapeutic time window of minocycline application for VaD (Ma et al., 2015).

In addition to minocycline, functional improvement via an anti-inflammatory drug dimethyl fumarate was demonstrated in mouse model of VaD (Fowler et al., 2018). Interestingly, the administration of this agent restored white mater function through attenuating microgliosis in response to hypoperfusion (Fowler et al., 2018).

6.2. Promotion of microglial M1-to-M2 shift

Restoration of microenvironmental homeostasis appears to be important for ameliorating neuronal damage following hypoperfusion (Chen et al., 2015). Disequilibrium in microglial M1/M2 phenotype is a prominent pathological feature in VaD rodents, it is therefore plausible that medications that enhancing the microglial M1-to-M2 shift may facilitate the reduced neuronal injury and cognitive deficits. Cannabinoid signaling pathway plays a pivotal role in regulating neuroinflammation. Several animal and cell culture studies indicated that activation of cannabinoid receptor 2 (CB_2R) aided in shifting the deleterious M1 toward the protective M2 phenotype (Correa et al., 2010; Ehrhart et al., 2005; Luo et al., 2018). CB_2R agonists such as paeoniflorin (Luo et al., 2018) and 1-phenylisatin (Jayant and Sharma, 2016) have been proven to provide valuable benefits for the alleviation of learning and memory decline in animal model of VaD.

Mammalian target of rapamycin (mTOR) signal governs microglial function and also drives vascular dysfunction in age-related pathological conditions (Hu et al., 2020; Keane et al., 2021). mTOR inhibitor everolimus is a U.S. Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved anti-cancer drug. It balanced the microglial M1/M2 polarization by converting M1 microglia into the M2 phenotype and ameliorated cognitive decline in hypoperfused mice (Chen et al., 2016b). Rapamycin, another clinically approved immunosuppressant targeting mTOR inhibition, has also been implicated to restore neurovascular function in AD model mice as well as mice with cognitive dysfunction and atherosclerosis (Jahrling et al., 2018; Lin et al., 2013). Considering this reagent may extend lifespan, there is a great potential for drug repurposing in the treatment of neurovascular disorders, such as VaD.

Besides, leptin exacerbated hypoxia-induced generation of pro-inflammatory cytokines from microglia, whereas depletion of leptin receptor favored the M1 to M2 phenotype switch of cerebral microglia and thus attenuated mouse cognitive deficits caused by hypoperfusion (Du et al., 2020). Similar results were obtained in mice deficient in microglial voltage-gated proton channel Hv1 (Yu et al., 2020).

6.3. *Inhibition of pro-inflammatory cytokines*

Being a vital pro-inflammatory cytokine, TNF-α modulates inflammatory responses in wide spectrum of human diseases. Currently, anti-TNF-α therapies are widely used for the treatment of autoimmune inflammatory disorders. A remarkably high level of TNF-α was detected in cerebrospinal fluid of VaD patients (Tarkowski et al., 1999). Microglia are the principal source of TNF-α (Welser-Alves and Milner, 2013), while the excessive release of this cytokine potentiates microglial activation via an autocrine mechanism (Bras et al., 2020; Kuno et al., 2005). Therefore, neutralization of TNF-α or blockage of TNF-α receptor may ameliorate microglial activation and neuronal damage in dementia. To support this notion, administration of adalimumab, a TNF-α inhibitor, reversed the microglial M1/M2 polarization, suppressed neuroinflammation and improved memory impairments in rats following hypoperfusion (Xu et al., 2021). Similarly, the use of antibodies or biologics that counteract TNF-α exerts beneficial effects in memory and cognitive performance of AD model animals (Detrait et al., 2014; Park et al., 2019). Moreover, a recent study shows that neutralization of IL-1β with an anti-IL-1β antibody prevented both white matter and gray matter injury in hypoperfused mice (Quintana et al., 2021). Nevertheless, clinical trial is lacking.

7. Conclusions and perspectives

Recent advances in the pathologic progression of VaD have highlighted a contributing role of microglia within the microenvironment of brain. Cerebral microglia exhibit highly dynamic motility, possess diverse functions, and interact with multiple types of cells in response to environmental changes or stimuli. A better understanding of the spatiotemporal pattern of microglia-modulated neuroinflammation in disease pathogenesis is needed. To date, some of the therapeutic options targeting microglia have been proposed in animal models, while the efficacy still requires to be verified in clinical trials. Also, there is growing interest in non-drug therapies as promising intervention for cognitive decline in VaD. Some rodent studies indicate that lifestyle modifications, such as physical exercise and dietary control, also prevent microglial activation, attenuate neuroinflammation, and improve cognitive function (Hu et al., 2019; Trigiani et al., 2019). Future investigation in this regard may broaden our understanding of the role of microglia in VaD.

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