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Review Article

The pericyte–glia interface at the blood–brain barrier

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The cerebrovasculature is a multicellular structure with varying rheological and permeability properties. The outer wall of the brain capillary endothelium is enclosed by pericytes and astrocyte end feet, anatomically assembled to guarantee barrier functions. We, here, focus on the pericyte modifications occurring in disease conditions, reviewing evidence supporting the interplay amongst pericytes, the endothelium, and glial cells in health and pathology. Deconstruction and reactivity of pericytes and glial cells around the capillary endothelium occur in response to traumatic brain injury, epilepsy, and neurodegenerative disorders, impacting vascular permeability and participating in neuroinflammation. As this represents a growing field of research, addressing the multicellular reorganization occurring at the outer wall of the blood-brain barrier (BBB) in response to an acute insult or a chronic disease could disclose novel disease mechanisms and therapeutic targets.

The multicellular assembly at the abluminal–cerebrovascular interface

Accumulating evidence advocates for a role of cerebrovascular dysfunction in central nervous system (CNS) diseases, negatively impacting neurovascular coupling and neurophysiology [1-8]. We here focus on capillary blood–brain barrier (BBB) and the abluminal compartmentwhere pericytes and astrocyte end feet coexist to maintain the barrier's properties [9]. We specify that the terms abluminal, perivascular, or outer wall will be generally used to identify cells: (i) residing around the capillary endothelium, (ii) anatomically adhering to the endothelial cells or the basal membrane, (iii) and existing within the perivascular cuff. At the capillary level, pericytes and astrocyte end-feet are structurally intertwined, enveloping the outer endothelial wall (Figure 1, *authors' images*). This unique anatomical assembly of cells is strategic, allowing the communication of pericytes with the endothelial cells and the parenchymal glia (e.g., astrocytes and microglia) during health and disease conditions (Figure 1A, B-B1). Pericytes outline 60–70% of the abluminal endothelial surface, with astrocyte end-feet completing the coverage and overlaying pericytes (Figure 1B2). Pericytes are identified based on their round soma and thin ramifications lining the endothelium (Figure 1A,C). An array of markers (e.g. platelet-derived growth factor receptor β, CD13, desmin etc.), transgene NG2 constructs (Figure 1), and the fluoro-Nissl dye [10] are used to recognize pericytes. The intimate endothelial–pericyte–astrocyte assembly is maintained by the basal lamina and regulated at the cellular level by a machinery of junction proteins, including connexins and N-cadherins (see [2,11-14] for details). Figure 1C-C1 (*authors' unpublished observations*) shows neighboring pericyte-microglial cells *in vivo* in the brain. The significance and the exact molecular cross-talk existing between pericytes and microglial cells in physiological and disease conditions remain to be elucidated.

Understanding the multicellular reactivity and plasticity occurring around the capillary endothelium during CNS diseases is important to develop BBB repair strategies (Figure 2A). It has been proposed

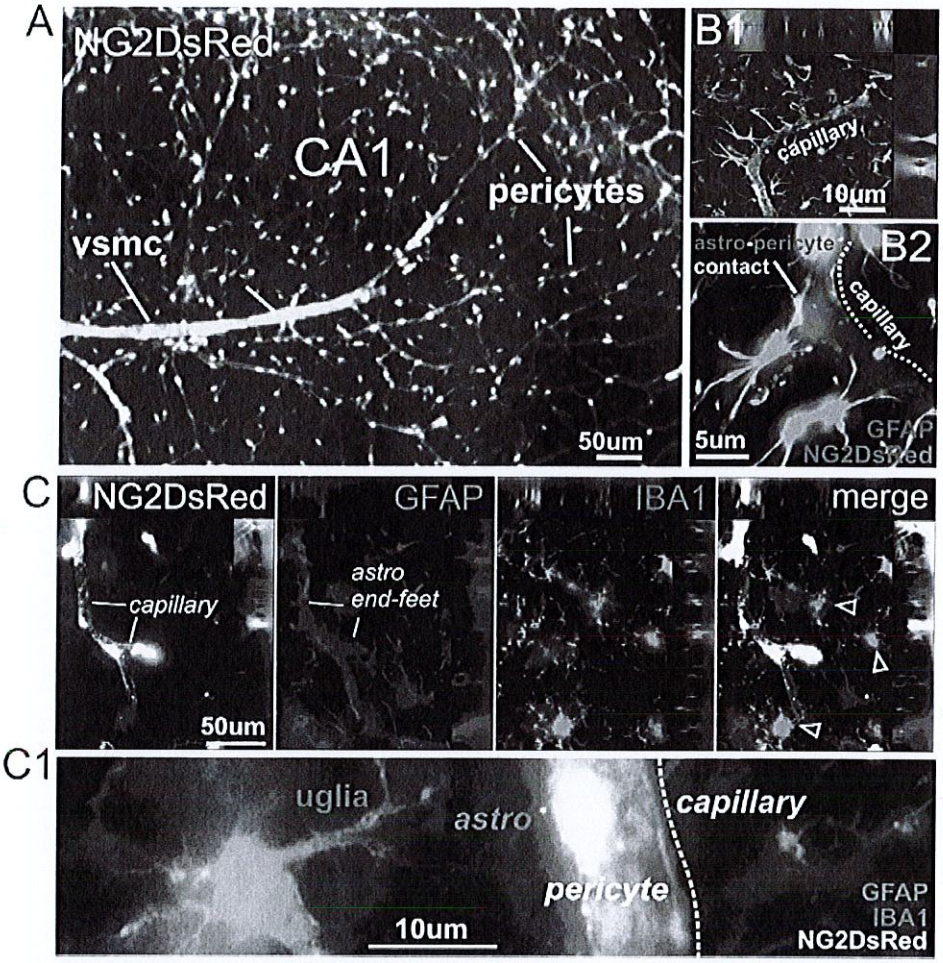


Figure 1. Pericyte–glia structures at the capillary BBB

(**A**) Pericytes are emerging players in cerebrovascular biology. Pericytes (NG2DsRed) envelope the abluminal side of arterioles and capillaries, while smooth muscle cells control the tone of larger vessels (e.g. arteries). (**B1**,**B2**) Astrocyte end-feet and pericytes are in direct contact, defining capillary properties and integrity. (**C**,**C1**) The pericyte–astrocyte–microglial complex. Three cell types are anatomically positioned within a 10–20 micrometers distance one from another and at the outer endothelial wall. Microglial cells are parenchymal (*arrowheads*) and proximal to the capillaries, possibly playing distinct roles during physiological and pathological conditions (*authors' previously unpublished images*).

that sealing a leaky BBB may decrease the accumulation of blood-derived products (Figure 2A) into the brain parenchyma, rectifying the neurovascular system toward a physiological interstitial homeostasis. The latter could improve the efficacy of neuronal drugs (Figure 2B) [4,6,15]. In general, capillary damage follows a sterile injury (e.g. status epileptics, non-penetrating trauma, and vascular accident), develops during disease progression or lingers during chronic pathological stages [16,17]. The inflammatory response accompanying CNS pathologies promotes an aberrant neuro-vascular remodeling [18,19], formation of scar tissue [20,21], and neuronal dysfunction [22]. In case of the pericyte–endothelium interface, the platelet-derived growth factor receptor signaling (PDGFRβ/PDGF-BB), transforming growth factor β (TGF-β), and the Notch pathway have been proposed as potential targets to modulate BBB stability and, perhaps, inflammation [2]. Early targeting of BBB damage and neuroinflammatory process may be disease modifying, whereas the importance of controlling inflammation may be different when chronic pathological stages are established (Figure 2B).

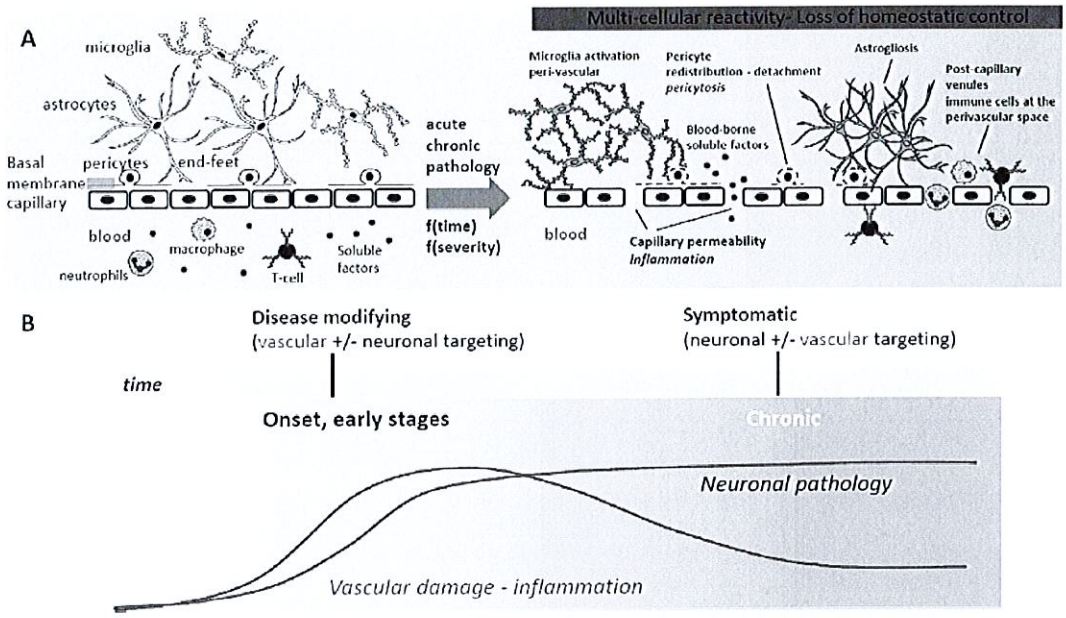


Figure 2. Multicellular deconstruction at the cerebrovascular interface, potential impact of neurovascular targeting, and modulation of neuroinflammation.

(**A**) Cell redistribution around the BBB endothelium during disease conditions. Under physiological conditions (left), astrocytes and pericytes contribute to capillary stability and interendothelial tightness. The stringent permeability at the BBB is crucial for the segregation between the peripheral circulation (blood) and the CNS. Following an acute event (traumatic brain injury, stroke, status epilepticus) or chronic disease (epilepsy, Alzheimer's disease), a multicellular disarray and reactivity occur (as a function of time and severity of the pathology) around the capillary endothelium and at the post-capillary venules. A number of immune molecules can activate pericytes that, in turn, can acquire an inflammatory phenotype (see Table 1). (**B**) Neurovascular targeting during disease progression. We hypothesize a vascular-inflammatory mechanism of disease during the early-mid stages of disease, promoting neuronal pathology. During chronic stages, the vascular inflammatory component may stabilize and neuronal dysfunction could become the main target. We hypothesize anti-inflammatory treatment (+/– accompanied with neuronal drugs) to be disease modifying at early-mid stages when inflammation and cerebrovascular damage unfold and develop.

Cell reactivity at the abluminal compartment: an overview

Pericytes display immune properties, responding to or contributing to inflammation *in vivo* [23-29] and *in vitro* (Table 1). Pericytes participate in both innate and adaptive immunity processes *in vivo* [23,24]. A significant number of *in vitro* studies point to the capacity of pericytes to act as immune cells. However, the ability of pericytes to maintain their properties *in vitro* remains uncertain. Thus, culture conditions (e.g. presence of serum proteins and growth factors) may have an impact on pericyte phenotype, introducing a bias and, perhaps, mimicking BBB damage and the access of serum components into the brain. *In vivo* studies are therefore relevant, especially if the aim is to compare the changes occurring amongst health and disease conditions. *In vivo* studies have shown pericyte modifications and reactivity in CNS pathologies associated with inflammatory changes, including ischemic stroke [25,26], Alzheimer's disease (AD) [15,27], status epilepticus [28], and traumatic brain injury [29]. Similar considerations apply to peripheral CNS pathologies such as spinal cord injury [30].

Pericytes are required for neutrophil trafficking across the endothelium *in vivo* [31]. Due to their position at the outer endothelial wall, pericytes can react to immune stimuli coming from brain resident glial cells or from circulating leukocytes accessing the perivascular space of post-capillary venules during disease conditions [32-35]. Amongst the immune challenges impacting pericytes we here report (see Table 1):

Pericytes and cytokines

(i) *TNFα*: upon TNFα stimulation pericytes release metalloproteinases (MMP-9), impacting BBB integrity [36-38].
(ii) *IL-1β*: human pericytes exposed to IL-1β overexpress adhesion molecules (intercellular adhesion molecule-1 (ICAM-1)), interleukin-8, monocyte chemoattractant protein-1 (MCP-1), and IL-1β itself [39,40]. TNF-α, IL-1β,

Table 1 Evidence supporting a role of pericytes in neurovascular inflammation

Stimuli	Pericyte response	References
LPS	CXCL10, CCL20, CXCL8, CXCL1, IL-6, CCL2, CXCL2, CXCL3, CCL3, CCL4	[23]
IL-1β	Neutrophils chemo-attraction, IL-1β, IL-8, attenuate COX-2 and SOD-2, ICAM-1, αSMA	[164,39,41]
TNF-α	Pericyte migration, microglial activation, neutrophils chemo-attraction, IL-1β, MMP-9	[42,164,165,37]
IFN-γ	PDGFRβ, HLA expression, MHC II, IP-10, CD68	[56,166,23]
TGF-β1	Anti-inflammatory phenotype, CX3CL1, down-regulation of CD36, CD47, CD68, NOX4, COX-2, MMP-2	[42,23,167]
LPS, TNF-α, IL-1β, IFNγ, and IL-6	iNOS	[168]
LPS, TNF-α, IL-1β	NFκB translocation	[23,169]
TNF-α, IL-1β/TGF-β1	IL-6	[42,43]
Ros production	Stellate morphology	[44]
O_2 deprivation	Reduction in CD13, αSMA, PDGFRβ shedding, and enhanced microglia markers (IBA1, MHC II, CD11b, CD68)	[170]

Abbreviations: aSMA: alpha smooth muscle actin; CCL: chemokine (C-C motif)ligand; COX-2, cyclooxygenase-2; CXCL: chemokine (C-X-C motif) ligand; HLA: human leukocyte antigen; ICAM-1: intercellular adhesion molecule-1; IBA: ionized calcium binding adaptor molecule 1; IFNγ; interferon γ; IL-6: interleukin 6; iNOS: inducible nitric oxide synthase; IP-10: interferon gamma-induced protein 10; LPS: lipopolysaccharide; MCH: major histocompatibility complex; MMP: metalloproteinase; NFkB: nuclear factor kappa; ROS: reactive oxygen species; SOD: superoxide dismutase; TNFa: tumor necrosis factor alpha;

and interferon γ (IFNγ) promote inducible nitric oxide synthase (iNOS) in porcine and rat pericytes [40-42]. (iii) *IFNγ* and*TGF-β1*: IFNγ induces human leukocyte antigen (HLA) expression, the latter blocked by TGF-β1 [43]. Human pericytes react to TGF-β1modifying the expression of a panel of immune-related genes, e.g. increasing NOX4, cyclooxygenase-2 (COX-2), IL-6, and MMP-2 or decreasing IL-8, CX3CL1, MCP1, and vascular adhesion molecule-1 (VCAM-1) expression. TGF-β1 impacts the expression of chemokines and adhesion molecules in pericytes, possibly influencing leukocyte trafficking [43].

Pericytes and immune cells

(i) Pericytes are involved in lymphocyte and neutrophil transmigration across the brain endothelium through IFNγ or TNFα stimulation. The latter factors up-regulate ICAM-1, VCAM-1, and MHC I [35,44]. Macrophage-like properties have been attributed to pericytes, e.g. pinocytosis and phagocytosis of latex beads [43]. A number of macrophage-like markers have been reported in pericytes during inflammation, including MHC-II, CD11b, CD36, CD68, or CD163 [23,40]. Human pericytes display phagocytic traits in response to LPS, TNF-α, or IL-1β stimulation, producing macrophage-like molecules such as MCP-1, IL-8, or metalloproteases [43]. *In vitro*, mouse pericytes display features of multipotent stem cells [45]. Finally, the cross-talk between T cells and pericytes has been suggested to favor the induction of allogeneic $CD25^{high}/FoxP3^{+}$ regulatory CD4 cells. [46].

Astrocyte–pericyte communication

Astrocyte end-feet and pericytes are anatomically connected [2,47,48] and their cross-talk occur during development and inflammation [49,50]. During angiogenesis, astrocytes and pericytes participate in the deposition of the basal lamina [51-53]. Astrocytes were hypothesized to induce the synthesis of fibronectin by pericytes [54]. Astrocytes and pericytes are involved in the developmental localization and polarization of ATP-binding cassette transporters on endothelial cells [48]. However, the pericyte–astrocyte interplay occurring in the healthy and pathological adult brain remains largely understudied.

Cerebrovascular cell modifications and disassembly during CNS pathology

Addressing the cellular changes occurring around the capillary endothelial wall is important to outline the mechanisms of cerebrovascular damage in disease conditions. We here provide evidence for endothelial, pericytes, and glial cell changes occurring in traumatic brain injury (TBI), epilepsy, Alzheimer's disease (AD), and ageing.

Acute and long-term cerebrovascular cell changes occurring post-TBI

TBI is not a transient event but rather a disease process [55] as TBI patients present long-lasting neurological consequences [56-60]. TBI pathophysiology includes [61]: (i) a primary injury resulting from a mechanical impact causing damage to the neurovascular structures; (ii) a secondary injury with formation of edema, decreased cerebral perfusion, increased glutamate levels, excitotoxicity, and BBB dysfunction that can last from days to years [5,61-68]. Intracerebral hemorrhage and microbleeding can increase intracranial pressure (ICP) and the likelihood of vasogenic edema, while the *heme* group entering the brain can promote oxidative stress and inflammation [69].

Perivascular cells undergo pathological changes and reactivity shortly post TBI. Pericytes migrate away from the endothelial wall after brain trauma [70]. The molecular mechanisms underscoring pericyte–endothelial pathology post TBI are, however, not completely understood. PDGFRβ has been proposed to be involved in tissue or cell remodeling after brain injury, including a biphasic pericyte loss and reactivity pattern [25,29]. Interestingly, treatment with a CO-releasing molecule (CORM)-3 was shown to reduce pericyte death after TBI with beneficial effects on neurological deficits [71]. Changes in cell-to-cell communication at the cerebrovasculature also involve astrocytes, with increased MMP secretion acting on the endothelial tight junctions. The expression of MMP post TBI [72,73]triggers the degradation of the extracellular matrix and weakens barrier structures [74-77].

Infiltration of blood-borne molecules, such as albumin, draws water into the brain parenchyma across the capillary wall, favoring post-TBI epilepsy or neurodegenerative processes [78-83]. However, a structural BBB opening is not always necessary for the permeability to be increased, as transcytosis mechanisms could take the relay [84-86]. For instance, increased Caveolin-1 (Cav-1) expression has been reported in animal models of brain injuries [81,84,87,88]. Caveolins not only contribute to transport functions but also influence the lipid raft structures and regulate the activity of the endothelial nitric oxide synthase (eNOS) [89,90]. Cav-1 stabilizes tight junctions [91] and regulates the activity of the drug-efflux p-glycoprotein (P-gP) [92], as demonstrated by the increase in Cav-1 and P-gP expression 1 week post TBI in rats [81].

TBI also results in long-lasting pathophysiological brain changes [93]. BBB permeability is increased in the majority of mild-TBI subjects that experience a seizure or develop epilepsy after the injury [94]. Multifocal and perivascular IgG staining was found in the gray matter of TBI subjects deceased between 1 and 47 years after the initial injury [66]. Long-term BBB changes were also found in animal models of TBI. IgG staining was visualized in the corpus callosum 3 months after the injury [95]. Increased expression of perlecan and fibronectin and decreased capillary diameter were reported [5,64]. Moreover, the levels of Cav-1 were increased in cortical vessels 2 months post injury [96,97]. Interestingly, increased amyloid depositions were found at the cerebral vesselssuggesting a failing vascular mechanism of interstitial waste clearance. Decreased P-gP expression was proposed as a contributing mechanism [64]. A better understanding of the cerebrovascular cell changes occurring long-term after TBI is important to improve disease management and pharmacology.

Epilepsy as a cerebrovascular dysfunction: an update

The evidence of cerebrovascular mechanisms of epilepsy is overwhelming and has been previously addressed [8,98-100]. A neurovascular approach to epilepsy has disclosed a number of entry points to decipher disease mechanisms. Neurovascular coupling is the key in the epileptic brain as ictal-to-interictal neuronal transitions are synchronized to metabolic changes contingent on oxygenation and regional blood flow. The latter depends on the cellular interplay occurring in the cerebrovascular compartment. Status epilepticus (SE) promotes pericytes and astrocytes activation at the endothelium, negatively impacting the barrier's properties and possibly reiterating the epileptic pathology [101]. NG2DsRed pericyte plasticity or ectopic coverage was reported after SE in an experimental model [28,102]. Recent evidence has shown that hypoperfusion and hypoxia occurring after focal seizures are responsible for cell damage, behavioral changes, or comorbidities [100]. From a mechanistic standpoint, inhibition of COX-2 and L-type calcium channels was sufficient to prevent postictal cerebrovascular changes. The latter findings are remarkable as cerebrovascular mechanisms of seizures may overlap, at least in part, with those reported in brain ischemia. The latter could allow a transdisciplinary use of diagnostic imaging to monitor cerebrovascular perfusion, oxygenation, and reactivity [8,98]. A number of reports have suggested the utility of radiological biomarkers of BBB damage as diagnostic or prognostic means in epilepsy [103,104]. The functional involvement of perivascular cells, in particular pericytes and smooth muscle cells, remains to be determined as they could control ictal perfusion changes.

Cerebrovascular cell changes and inflammation in AD

Amyloid plaques, extracellular aggregates of fibrillary amyloid-β (Aβ) protein, and neurofibrillary tangles are traits of AD [105-107]. Accumulating clinical and experimental evidence demonstrate a role of cerebrovascular dysfunction

and inflammation in AD, supporting the hypothesis of sporadic AD as a neurovascular disease [107-114]. Disease conditions bearing an important cerebrovascular component (e.g. diabetes mellitus, thrombotic episodes, high fibrinogen concentrations, or atherosclerosis) are risk factors for AD [115-117]. Interestingly, measuring cerebral blood flow has been proposed as a diagnostic tool to identify preclinical AD stages [114,118]. A recent study [119] indicates early cerebrovascular abnormalities in AD, advocating for a biomarker of disease progression.

Pericytes detachment and ectopic coverage of the outer cerebrovascular wall occur during AD progression [2,120]. Pericyte pathology impacts capillary integrity, potentially facilitating the accumulation of toxic molecules in the brain parenchyma and subsequent neurodegenerative changes [27,121-124]. Available evidence points to modifications in the pericyte–endothelial PDGFRβ/PDGF-BB signaling as a mechanism of vascular damage. *In vivo* studies have shown that an impaired PDGFRβ signaling is associated with pericyte damage and BBB dysfunction, facilitating neurodegenerative changes. Reduced Aβ clearance, resulting from BBB breakdown, was proposed as a contributing mechanism of AD progression. See [2,120] for details.

Microglial cells are involved in the inflammatory response occurring in the AD brain (hippocampus, Figure 3A-A1) [15,125,126]. Figure 3B-B1 shows an overview of the hippocampal microglial cell changes in human AD. Clusters of amoeboid microglia and Aβ are common (Figure 3C-C1). Our previously unpublished data also indicate accumulation of IgG around the capillaries (Figure 3D), suggesting BBB permeability. In experimental AD, microglial cells accumulate around the capillaries (*unpublished observations* in Figure 3E and [27]). Although unfrequent, instances of Aβ accumulation at the capillaries can be found (Figure 3E1). Interestingly, the role of microglial cells in AD remains controversial. Initially considered as a pathophysiological component associated with a negative outcome, recent evidence has instead proposed a more beneficial effect, possibly through amyloid plaque digestion [125,127-129]. Remarkably, a recent report showed no changes in microglia proliferation during AD progression in a cohort of human brains as compared with available control [130]. The latter findings are not immediately comparable with genetic models of AD where incremental glial inflammation is reported [27,33].

Microglial cells can induce astrocyte activation *in vivo* and *in vitro* [131]. The resulting astrocyte phenotype is dependent on the pathological insult. Briefly, astrocytes can be classified as A1 and A2, implicated respectively in neuronal damage and repair. Neurodegenerative disorders are associated with damaging A1 astrocytes [131]. The impact of a microglia-mediated immune response in AD development was recently highlighted in association with TREM2 variants, a surface receptor that modulates the microglia phenotype [132-134]. Genetic screening of a large cohort of patients linked rare variants of microglial genes, including TREM2, to AD [134]. Finally, a link between the ApoE4 isoform, an AD risk factor, and BBB integrity was demonstrated [135,136]. ApoE4 does not maintain low levels of cyclophilin-A (Cyc-A), a cytokine that induces BBB damage. Thus, under physiological conditions, astrocytes release ApoE isoform 3 inhibiting Cyc-A via LRP-1 receptors, while the presence of ApoE4 leads to the failure of this control mechanism [135,137,138]. Although controversial, the involvement of astrocytes in AD may also encompass a mechanism of interstitial clearance [123,139].

Cerebral amyloid angiopathy and the perivascular cells

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of Aβ primarily on cortical and leptomeningeal arteries [140-143]. As larger brain vessels are involved in the regulation of the cerebrospinal or interstitial fluid circulation, CAA could impact amyloid clearance mechanisms [144], e.g. via the lymphatic system [123,145]. Recent evidence supports a role for the *clusterin* gene in AD and CAA pathophysiology [146]. When clusterin is absentAβ clearance by perivascular drainage becomes predominant, resulting in less parenchymal plaques but exacerbating CAA [146]. During the formation of vascular amyloidosis, the glio-vascular unit is compromised with a reported physical separation of the astrocytic end-feet from the endothelium. Although astrocytes may continue releasing vasoactive substances, the vascular amyloid determines vessel stiffness [145]. Progression of capillary pathology and CAA have also been found in the 5xFAD mouse model of AD [27]. In the latter case, amyloid accumulation at the parenchymal capillaries is sporadic (example in Figure 2E1) while amyloid proteins are positioned along larger vascular structures, further supporting a pathological link between CAA and AD [147].

The cerebrovasculature during ageing

Cerebrovascular modifications are reported during ageing. Doppler studies [148,149] and PET imaging [150] have shown a reduction in cerebral blood flow in elderly subjects [151]. Reduced microvessel density has been reported with ageing in the cortex [152,153] and the hippocampus [154-156]. Microvascular rarefaction may result from age-dependent apoptosis, as observed in animal models [157]where oxidative stress and chronic inflammation could

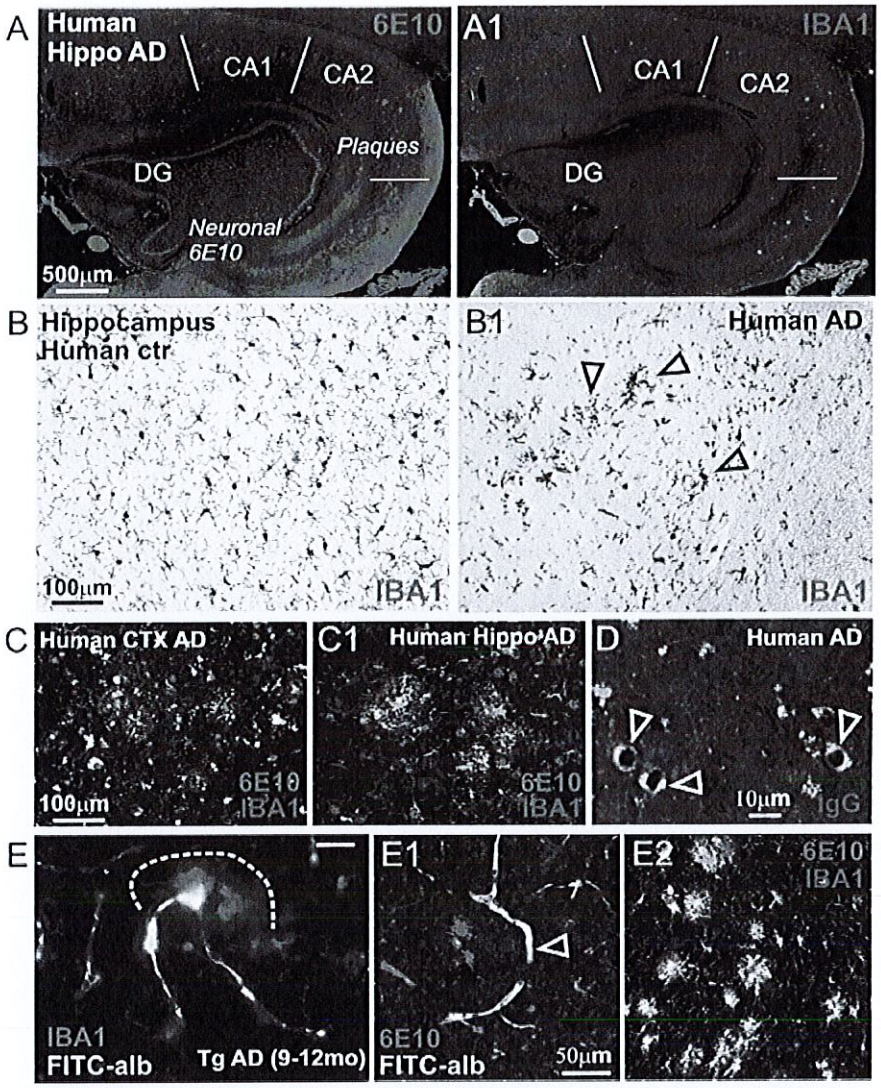


Figure 3. Examples of neuroinflammation and cerebrovascular changes in human and experimental AD

(**A**,**A1**) Montage of human hippocampi to show plaques and microglial distribution in AD. (**B**) Uniformly distributed microglial cells in control human tissue. (**B1**) Post-mortem AD brain shows aggregates (periplaque or perivascular; *arrows*) of IBA1 microglial cells. (**C**,**C1**) Examples of plaque–microglial aggregates in human AD (cortex and hippocampus). (**D**) IgG perivascular accumulation is a sign of BBB damage. (**E**,**E1**) Perivascular pathology (microglial clustering, dotted line in (E); perivascular β amyloid, arrows in (E1)) is observed in an experimental model of AD . (**E2**) Topographic correspondence between microglia and $6E10^{+}$ amyloid in the parenchyma (*authors' unpublished images and observations*).

be contributing factors. Additional studies have shown an increase in vessel tortuosity of penetrating arterioles [156,158,159] and abnormal BBB tight junctions expression at the capillaries in white matter lesions [160].

A recent study [161] indicated the occurrence of BBB damage in the hippocampal CA1 and dentate gyrus regions during ageing. From a cellular standpoint, a link between cognitive decline and pericyte pathology during ageing has been proposed [114,121]. In particular, $PDGFR\beta^{+/-}$ mice displayed accumulation of perivascular fibrin with age as compared with wild-type animals. The age-dependent pericyte-vascular damage preceded neuronal pathophysiology [121]. As pericytes control capillary diameter their loss, or modification, could impact neurovascular coupling [122,162,163]. The cerebrovascular pathological signs observed during ageing could represent a factor aggravating other pathologies, e.g. AD progression or the outcome of stroke accidents.

Future directions

Despite of the accumulating evidence, it remains unclear how pericytes communicate with astrocytes and microglial cells *in vivo* and, amongst these cells, who plays a major role in initiating, or coordinating, a pathological cerebrovascular inflammatory response. It remains to be defined whether genetic modifications occurring at the perivascular cells may constitute clinically significant risk factors for neuropathophysiology. If fully elucidated, the players governing the abluminal cerebrovascular assembly in health and disease may be exploited to develop new therapeutic approaches to treat CNS diseases.

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Competing interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

AD, Alzheimer's disease; Aβ, amyloid-β; BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; Cav-1, Caveolin-1; CNS, central nervous system; COX-2, cyclooxygenase-2; Cyc-A, cyclophilin-A; ICAM-1, intercellular adhesion molecule-1; IFNγ, interferon γ; MCP-1, monocyte chemoattractant protein-1; MMP, metalloproteinase; PDGFRβ, platelet-derived growth factor receptor β; P-gP, p-glycoprotein; SE, status epilepticus; TBI, traumatic brain injury; TGFβ, transforming growth factor β; VCAM-1, vascular adhesion molecule-1.

References

1 Altman, R. and Rutledge, J.C. (2010) The vascular contribution to Alzheimer's disease. *Clin. Sci. (Lond.)* **119**, 407–421

2 Sweeney, M.D., Ayyadurai, S. and Zlokovic, B.V. (2016) Pericytes of the neurovascular unit: key functions and signaling pathways. *Nat. Neurosci.* **19**, 771–783, https://doi.org/10.1038/nn.4288

3 Wilhelm, I., Nyúl-Tóth, Á, Suciu, M., Hermenean, A. and Krizbai, I.A. (2016) Heterogeneity of the blood-brain barrier. *Tissue Barriers* **4**, e1143544, https://doi.org/10.1080/21688370.2016.1143544

4 Marchi, N., Banjara, M. and Janigro, D. (2016) Blood-brain barrier, bulk flow, and interstitial clearance in epilepsy. *J. Neurosci. Methods* **260**, 118–124, https://doi.org/10.1016/j.jneumeth.2015.06.011

5 Jullienne, A., Roberts, J.M., Pop, V., Paul Murphy, M., Head, E., Bix, G.J. et al. (2014) Juvenile traumatic brain injury induces long-term perivascular matrix changes alongside amyloid-beta accumulation. *J. Cereb. Blood Flow Metab.*, http://www.ncbi.nlm.nih.gov/pubmed/25052558, https://doi.org/10.1038/jcbfm.2014.124

6 Abbott, N.J. and Friedman, A. (2012) Overview and introduction: the blood-brain barrier in health and disease. *Epilepsia* **53** (Suppl. 6), 1–6, https://doi.org/10.1111/j.1528-1167.2012.03696.x

7 Abbott, N.J., Revest, P.A. and Romero, I.A. (1992) Astrocyte-endothelial interaction: physiology and pathology. *Neuropathol. Appl. Neurobiol.* **18**, 424–433, https://doi.org/10.1111/j.1365-2990.1992.tb00808.x

8 Librizzi, L., de Cutis, M., Janigro, D., Runtz, L., de Bock, F., Barbier, E.L. et al. (2017) Cerebrovascular heterogeneity and neuronal excitability. *Neurosci. Lett.*, https://doi.org/10.1016/j.neulet.2017.01.013

9 Abbott, N.J., Patabendige, A.A.K., Dolman, D.E.M., Yusof, S.R. and Begley, D.J. (2010) Structure and function of the blood-brain barrier. *Neurobiol. Dis.* **37**, 13–25, https://doi.org/10.1016/j.nbd.2009.07.030

10 Damisah, E.C., Hill, R.A., Tong, L., Murray, K.N. and Grutzendler, J. (2017) A fluoro-Nissl dye identifies pericytes as distinct vascular mural cells during in vivo brain imaging. *Nat. Neurosci.* **20**, 1023–1032, https://doi.org/10.1038/nn.4564

11 Liu, W.-Y., Wang, Z.-B., Zhang, L.-C., Wei, X. and Li, L. (2012) Tight junction in blood-brain barrier: an overview of structure, regulation, and regulator substances. *CNS Neurosci. Ther.* **18**, 609–615, https://doi.org/10.1111/j.1755-5949.2012.00340.x

12 Wolburg, H. and Lippoldt, A. (2002) Tight junctions of the blood-brain barrier: development, composition and regulation. *Vasc. Pharmacol.* **38**, 323–337, https://doi.org/10.1016/S1537-1891(02)00200-8

13 Bauer, H.-C., Krizbai, I.A., Bauer, H. and Traweger, A. (2014) "You Shall Not Pass"–tight junctions of the blood brain barrier. *Front. Neurosci.*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253952/, https://doi.org/10.3389/fnins.2014.00392

14 Thomsen, M.S., Routhe, L.J. and Moos, T. (2017) The vascular basement membrane in the healthy and pathological brain. *J. Cereb. Blood Flow Metab.*, https://doi.org/10.1177/0271678X17722436

15 Zlokovic, B.V. (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat. Rev. Neurosci.* **12**, 723–738

16 Corps, K.N., Roth, T.L. and McGavern, D.B. (2015) Inflammation and neuroprotection in traumatic brain injury. *JAMA Neurol.* **72**, 355–362, https://doi.org/10.1001/jamaneurol.2014.3558
17 Hinson, H.E., Rowell, S. and Schreiber, M. (2015) Clinical evidence of inflammation driving secondary brain injury: a systematic review. *J. Trauma Acute Care Surg.* **78**, 184–191, https://doi.org/10.1097/TA.0000000000000468
18 Hayakawa, K., Qiu, J. and Lo, E.H. (2010) Biphasic actions of HMGB1 signaling in inflammation and recovery after stroke. *Ann. N.Y. Acad. Sci.* **1207**, 50–57, https://doi.org/10.1111/j.1749-6632.2010.05728.x
19 Aihara, K., Mogi, M., Shibata, R., Bishop-Bailey, D. and Reilly, M.P. (2012) Inflammation and vascular remodeling. *Int. J. Vasc. Med.*, , https://www.hindawi.com/journals/ijvm/2012/596796/, https://doi.org/10.1155/2012/596796
20 Hesketh, M., Sahin, K.B., West, Z.E. and Murray, R.Z. (2017) Macrophage phenotypes regulate scar formation and chronic wound healing. *Int. J. Mol. Sci.* **18**, https://doi.org/10.3390/ijms18071545
21 Kim, J.Y., Park, J., Chang, J.Y., Kim, S.-H. and Lee, J.E. (2016) Inflammation after ischemic stroke: the role of leukocytes and glial cells. *Exp. Neurobiol.* **25**, 241–251, https://doi.org/10.5607/en.2016.25.5.241
22 Glass, C.K., Saijo, K., Winner, B., Marchetto, M.C. and Gage, F.H. (2010) Mechanisms underlying inflammation in neurodegeneration. *Cell* **140**, 918–934, https://doi.org/10.1016/j.cell.2010.02.016
23 Navarro, R., Compte, M., Álvarez-Vallina, L. and Sanz, L. (2016) Immune regulation by pericytes: modulating innate and adaptive immunity. *Front. Immunol.* **7**, 480, https://doi.org/10.3389/fimmu.2016.00480
24 ElAli, A., Thériault, P. and Rivest, S. (2014) The role of pericytes in neurovascular unit remodeling in brain disorders. *Int. J. Mol. Sci.* **15**, 6453–6474, https://doi.org/10.3390/ijms15046453
25 Fernández-Klett, F., Potas, J.R., Hilpert, D., Blazej, K., Radke, J., Huck, J. et al. (2013) Early loss of pericytes and perivascular stromal cell-induced scar formation after stroke. *J. Cereb. Blood Flow Metab.* **33**, 428–439, https://doi.org/10.1038/jcbfm.2012.187
26 Özen, I., Deierborg, T., Miharada, K., Padel, T., Englund, E., Genové, G. et al. (2014) Brain pericytes acquire a microglial phenotype after stroke. *Acta Neuropathol.* **128**, 381–396, https://doi.org/10.1007/s00401-014-1295-x
27 Giannoni, P., Arango-Lievano, M., Neves, I.D., Rousset, M.-C., Baranger, K., Rivera, S. et al. (2016) Cerebrovascular pathology during the progression of experimental Alzheimer's disease. *Neurobiol. Dis.* **88**, 107–117, https://doi.org/10.1016/j.nbd.2016.01.001
28 Milesi, S., Boussadia, B., Plaud, C., Catteau, M., Rousset, M.-C., De Bock, F. et al. (2014) Redistribution of PDGFRβ cells and NG2DsRed pericytes at the cerebrovasculature after status epilepticus. *Neurobiol. Dis.* **71**, 151–158, https://doi.org/10.1016/j.nbd.2014.07.010
29 Zehendner, C.M., Sebastiani, A., Hugonnet, A., Bischoff, F., Luhmann, H.J. and Thal, S.C. (2015) Traumatic brain injury results in rapid pericyte loss followed by reactive pericytosis in the cerebral cortex. *Sci. Rep.* **5**, https://doi.org/0.1038/srep13497
30 Göritz, C., Dias, D.O., Tomilin, N., Barbacid, M., Shupliakov, O. and Frisén, J. (2011) A pericyte origin of spinal cord scar tissue. *Science* **333**, 238–242, https://doi.org/10.1126/science.1203165
31 Proebstl, D., Voisin, M.-B., Woodfin, A., Whiteford, J., D'Acquisto, F., Jones, G.E. et al. (2012) Pericytes support neutrophil subendothelial cell crawling and breaching of venular walls *in vivo*. *J. Exp. Med.* **209**, 1219–1234, https://doi.org/10.1084/jem.20111622
32 Zlokovic, B.V. (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* **57**, 178–201, https://doi.org/10.1016/j.neuron.2008.01.003
33 Engelhardt, B., Vajkoczy, P. and Weller, R.O. (2017) The movers and shapers in immune privilege of the CNS. *Nat. Immunol.* **18**, 123–131, https://doi.org/10.1038/ni.3666
34 Balabanov, R., Beaumont, T. and Dore-Duffy, P. (1999) Role of central nervous system microvascular pericytes in activation of antigen-primed splenic T-lymphocytes. *J. Neurosci. Res.* **55**, 578–587, https://doi.org/10.1002/(SICI)1097-4547(19990301)55:5%3c578::AID-JNR5%3e3.0.CO;2-E
35 Zenaro, E., Piacentino, G. and Constantin, G. (2016) The blood-brain barrier in Alzheimer's disease. *Neurobiol. Dis.*
36 Machida, T., Dohgu, S., Takata, F., Matsumoto, J., Kimura, I., Koga, M. et al. (2017) Role of thrombin-PAR1-PKCθ/δ axis in brain pericytes in thrombin-induced MMP-9 production and blood-brain barrier dysfunction *in vitro*. *Neuroscience* **350**, 146–157, https://doi.org/10.1016/j.neuroscience.2017.03.026
37 Takata, F., Dohgu, S., Matsumoto, J., Takahashi, H., Machida, T., Wakigawa, T. et al. (2011) Brain pericytes among cells constituting the blood-brain barrier are highly sensitive to tumor necrosis factor-α, releasing matrix metalloproteinase-9 and migrating *in vitro*. *J. Neuroinflammation* **8**, 106, https://doi.org/10.1186/1742-2094-8-106
38 Takeuchi, H., Jin, S., Wang, J., Zhang, G., Kawanokuchi, J., Kuno, R. et al. (2006) Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. *J. Biol. Chem.* **281**, 21362–21368, https://doi.org/10.1074/jbc.M600504200
39 Rustenhoven, J., Scotter, E.L., Jansson, D., Kho, D.T., Oldfield, R.L., Bergin, P.S. et al. (2015) An anti-inflammatory role for C/EBPδ in human brain pericytes. *Sci. Rep.* **5**, 12132, https://doi.org/10.1038/srep12132
40 Hurtado-Alvarado, G., Cabañas-Morales, A.M. and Gómez-Gónzalez, B. (2014) Pericytes: brain-immune interface modulators. *Front. Integr. Neurosci.*, , http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3887314/, https://doi.org/10.3389/fnint.2013.00080
41 Pieper, C., Marek, J.J., Unterberg, M., Schwerdtle, T. and Galla, H.-J. (2014) Brain capillary pericytes contribute to the immune defense in response to cytokines or LPS *in vitro*. *Brain Res.* **1550**, 1–8, https://doi.org/10.1016/j.brainres.2014.01.004
42 Matsumoto, J., Takata, F., Machida, T., Takahashi, H., Soejima, Y., Funakoshi, M. et al. (2014) Tumor necrosis factor-α-stimulated brain pericytes possess a unique cytokine and chemokine release profile and enhance microglial activation. *Neurosci. Lett.* **578**, 133–138, https://doi.org/10.1016/j.neulet.2014.06.052
43 Rustenhoven, J., Aalderink, M., Scotter, E.L., Oldfield, R.L., Bergin, P.S., Mee, E.W. et al. (2016) TGF-beta1 regulates human brain pericyte inflammatory processes involved in neurovasculature function. *J. Neuroinflammation* **13**, 37, https://doi.org/10.1186/s12974-016-0503-0

44 Quimby, S. and Fern, R. (2011) Novel morphological features of developing white matter pericytes and rapid scavenging of reactive oxygen species in the neighbouring endothelia. *J. Anat.* **219**, 65–77, https://doi.org/10.1111/j.1469-7580.2011.01373.x

45 Sakuma, R., Kawahara, M., Nakano-Doi, A., Takahashi, A., Tanaka, Y., Narita, A. et al. (2016) Brain pericytes serve as microglia-generating multipotent vascular stem cells following ischemic stroke. *J. Neuroinflammation* **13**, 57, https://doi.org/10.1186/s12974-016-0523-9

46 Domev, H., Milkov, I., Itskovitz-Eldor, J. and Dar, A. (2014) Immunoevasive pericytes from human pluripotent stem cells preferentially modulate induction of allogeneic regulatory T cells. *Stem Cells Transl. Med.* **3**, 1169–1181, https://doi.org/10.5966/sctm.2014-0097

47 Al Ahmad, A., Gassmann, M. and Ogunshola, O.O. (2009) Maintaining blood-brain barrier integrity: pericytes perform better than astrocytes during prolonged oxygen deprivation. *J. Cell. Physiol.* **218**, 612–622, https://doi.org/10.1002/jcp.21638

48 Al Ahmad, A., Taboada, C.B., Gassmann, M. and Ogunshola, O.O. (2011) Astrocytes and pericytes differentially modulate blood-brain barrier characteristics during development and hypoxic insult. *J. Cereb. Blood Flow Metab.* **31**, 693–705, https://doi.org/10.1038/jcbfm.2010.148

49 Paolinelli, R., Corada, M., Orsenigo, F. and Dejana, E. (2011) The molecular basis of the blood brain barrier differentiation and maintenance. Is it still a mystery? *Pharmacol. Res.* **63**, 165–171, https://doi.org/10.1016/j.phrs.2010.11.012

50 Herland, A., van der Meer, A.D., FitzGerald, E.A., Park, T.-E., Sleeboom, J.J.F. and Ingber, D.E. (2016) Distinct contributions of astrocytes and pericytes to neuroinflammation identified in a 3D human blood-brain barrier on a chip. *PLoS ONE* **11**, e0150360, https://doi.org/10.1371/journal.pone.0150360

51 Balabanov, R. and Dore-Duffy, P. (1998) Role of the CNS microvascular pericyte in the blood-brain barrier. *J. Neurosci. Res.* **53**, 637–644, https://doi.org/10.1002/(SICI)1097-4547(19980915)53:6%3c637::AID-JNR1%3e3.0.CO;2-6

52 del Zoppo, G.J. (2010) The neurovascular unit, matrix proteases, and innate inflammation. *Ann. N.Y. Acad. Sci.* **1207**, 46–49, https://doi.org/10.1111/j.1749-6632.2010.05760.x

53 Wolburg, H., Noell, S., Mack, A., Wolburg-Buchholz, K. and Fallier-Becker, P. (2009) Brain endothelial cells and the glio-vascular complex. *Cell Tissue Res.* **335**, 75–96, https://doi.org/10.1007/s00441-008-0658-9

54 Bonkowski, D., Katyshev, V., Balabanov, R.D., Borisov, A. and Dore-Duffy, P. (2011) The CNS microvascular pericyte: pericyte-astrocyte crosstalk in the regulation of tissue survival. *Fluids Barriers CNS* **8**, 8, https://doi.org/10.1186/2045-8118-8-8

55 Masel, B.E. and DeWitt, D.S. (2010) Traumatic brain injury: a disease process, not an event. *J. Neurotrauma* **27**, 1529–1540, https://doi.org/10.1089/neu.2010.1358

56 Smith, D.H., Johnson, V.E. and Stewart, W. (2013) Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat. Rev. Neurol.* **9**, 211–221, https://doi.org/10.1038/nrneurol.2013.29

57 Babikian, T., Merkley, T., Savage, R.C., Giza, C.C. and Levin, H. (2015) Chronic aspects of pediatric traumatic brain injury: review of the literature. *J. Neurotrauma* **32**, 1849–1860, https://doi.org/10.1089/neu.2015.3971

58 Himanen, L., Portin, R., Hamalainen, P., Hurme, S., Hiekkanen, H. and Tenovuo, O. (2011) Risk factors for reduced survival after traumatic brain injury: a 30-year follow-up study. *Brain Inj.* **25**, 443–452, https://doi.org/10.3109/02699052.2011.556580

59 Konrad, C., Geburek, A.J., Rist, F., Blumenroth, H., Fischer, B., Husstedt, I. et al. (2011) Long-term cognitive and emotional consequences of mild traumatic brain injury. *Psychol. Med.* **41**, 1197–1211, https://doi.org/10.1017/S0033291710001728

60 Roozenbeek, B., Maas, A.I. and Menon, D.K. (2013) Changing patterns in the epidemiology of traumatic brain injury. *Nat. Rev. Neurol.* **9**, 231–236, https://doi.org/10.1038/nrneurol.2013.22

61 Pop, V. and Badaut, J. (2011) A neurovascular perspective for long-term changes after brain trauma. *Transl. Stroke Res.* **2**, 533–545, https://doi.org/10.1007/s12975-011-0126-9

62 McGinn, M.J. and Povlishock, J.T. (2016) Pathophysiology of traumatic brain injury. *Neurosurg. Clin. N. Am.* **27**, 397–407, https://doi.org/10.1016/j.nec.2016.06.002

63 Prins, M., Greco, T., Alexander, D. and Giza, C.C. (2013) The pathophysiology of traumatic brain injury at a glance. *Model Mech.* **6**, 1307–1315, https://doi.org/10.1242/dmm.011585

64 Pop, V., Sorensen, D.W., Kamper, J.E., Ajao, D.O., Murphy, M.P., Head, E. et al. (2013) Early brain injury alters the blood-brain barrier phenotype in parallel with beta-amyloid and cognitive changes in adulthood. *J. Cereb. Blood Flow Metab.* **33**, 205–214, https://doi.org/10.1038/jcbfm.2012.154

65 Ojo, J.O., Mouzon, B., Algamal, M., Leary, P., Lynch, C., Abdullah, L. et al. (2016) Chronic repetitive mild traumatic brain injury results in reduced cerebral blood flow, axonal injury, gliosis, and increased T-Tau and Tau oligomers. *J. Neuropathol. Exp. Neurol.* **75**, 636–655, https://doi.org/10.1093/jnen/nlw035

66 Hay, J.R., Johnson, V.E., Young, A.M., Smith, D.H. and Stewart, W. (2015) Blood-brain barrier disruption is an early event that may persist for many years after traumatic brain injury in humans. *J. Neuropathol. Exp. Neurol.* **74**, 1147–1157

67 Narayan, R.K., Maas, A.I., Servadei, F., Skolnick, B.E., Tillinger, M.N., Marshall, L.F. et al. (2008) Progression of traumatic intracerebral hemorrhage: a prospective observational study. *J. Neurotrauma* **25**, 629–639, https://doi.org/10.1089/neu.2007.0385

68 Candefjord, S., Winges, J., Yu, Y., Rylander, T. and McKelvey, T. (2013) Microwave technology for localization of traumatic intracranial bleedings-a numerical simulation study. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2013**, 1948–1951

69 Hua, Y., Keep, R.F., Hoff, J.T. and Xi, G. (2007) Brain injury after intracerebral hemorrhage: the role of thrombin and iron. *Stroke* **38**, 759–762, https://doi.org/10.1161/01.STR.0000247868.97078.10

70 Dore-Duffy, P., Owen, C., Balabanov, R., Murphy, S., Beaumont, T. and Rafols, J.A. (2000) Pericyte migration from the vascular wall in response to traumatic brain injury. *Microvasc. Res.* **60**, 55–69, https://doi.org/10.1006/mvre.2000.2244

71 Choi, Y.K., Maki, T., Mandeville, E.T., Koh, S.-H., Hayakawa, K., Arai, K. et al. (2016) Dual effects of carbon monoxide on pericytes and neurogenesis in traumatic brain injury. *Nat. Med.* **22**, 1335–1341, https://doi.org/10.1038/nm.4188

72 Jia, F., Pan, Y.H., Mao, Q., Liang, Y.M. and Jiang, J.Y. (2010) Matrix metalloproteinase-9 expression and protein levels after fluid percussion injury in rats: the effect of injury severity and brain temperature. *J. Neurotrauma* **27**, 1059–1068, https://doi.org/10.1089/neu.2009.1067

73 Grossetete, M., Phelps, J., Arko, L., Yonas, H. and Rosenberg, G.A. (2009) Elevation of matrix metalloproteinases 3 and 9 in cerebrospinal fluid and blood in patients with severe traumatic brain injury. *Neurosurgery* **65**, 702–708, https://doi.org/10.1227/01.NEU.0000351768.11363.48

74 Higashida, T., Kreipke, C.W., Rafols, J.A., Peng, C., Schafer, S., Schafer, P. et al. (2011) The role of hypoxia-inducible factor-1alpha, aquaporin-4, and matrix metalloproteinase-9 in blood-brain barrier disruption and brain edema after traumatic brain injury. *J. Neurosurg.* **114**, 92–101, https://doi.org/10.3171/2010.6.JNS10207

75 Chodobski, A., Zink, B.J. and Szmydynger-Chodobska, J. (2011) Blood-brain barrier pathophysiology in traumatic brain injury. *Transl. Stroke Res.* **2**, 492–516, https://doi.org/10.1007/s12975-011-0125-x

76 Loane, D.J. and Kumar, A. (2016) Microglia in the TBI brain: the good, the bad, and the dysregulated. *Exp. Neurol.* **275**, 316–327, https://doi.org/10.1016/j.expneurol.2015.08.018

77 Summers, L., Kangwantas, K., Rodriguez-Grande, B., Denes, A., Penny, J., Kielty, C. et al. (2013) Activation of brain endothelial cells by interleukin-1 is regulated by the extracellular matrix after acute brain injury. *Mol. Cell. Neurosci.* **57**, 93–103, https://doi.org/10.1016/j.mcn.2013.10.007

78 Shlosberg, D., Benifla, M., Kaufer, D. and Friedman, A. (2010) Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nat. Rev. Neurol.* **6**, 393–403, https://doi.org/10.1038/nrneurol.2010.74

79 Morganti-Kossmann, M.C., Satgunaseelan, L., Bye, N. and Kossmann, T. (2007) Modulation of immune response by head injury. *Injury* **38**, 1392–1400, https://doi.org/10.1016/j.injury.2007.10.005

80 Tomkins, O., Friedman, O., Ivens, S., Reiffurth, C., Major, S., Dreier, J.P. et al. (2007) Blood-brain barrier disruption results in delayed functional and structural alterations in the rat neocortex. *Neurobiol. Dis.* **25**, 367–377, https://doi.org/10.1016/j.nbd.2006.10.006

81 Badaut, J., Ajao, D.O., Sorensen, D.W., Fukuda, A.M. and Pellerin, L. (2015) Caveolin expression changes in the neurovascular unit after juvenile traumatic brain injury: signs of blood-brain barrier healing? *Neuroscience* **285**, 215–226, https://doi.org/10.1016/j.neuroscience.2014.10.035

82 Lucke-Wold, B.P., Logsdon, A.F., Smith, K.E., Turner, R.C., Alkon, D.L., Tan, Z. et al. (2015) Bryostatin-1 restores blood brain barrier integrity following blast-induced traumatic brain injury. *Mol. Neurobiol.* **52**, 1119–1134, https://doi.org/10.1007/s12035-014-8902-7

83 Wen, J., Qian, S., Yang, Q., Deng, L., Mo, Y. and Yu, Y. (2014) Overexpression of netrin-1 increases the expression of tight junction-associated proteins, claudin-5, occludin, and ZO-1, following traumatic brain injury in rats. *Exp. Ther. Med.* **8**, 881–886, https://doi.org/10.3892/etm.2014.1818

84 Knowland, D., Arac, A., Sekiguchi, K.J., Hsu, M., Lutz, S.E., Perrino, J. et al. (2014) Stepwise recruitment of transcellular and paracellular pathways underlies blood-brain barrier breakdown in stroke. *Neuron* **82**, 603–617, https://doi.org/10.1016/j.neuron.2014.03.003

85 Haley, M.J. and Lawrence, C.B. (2017) The blood-brain barrier after stroke: Structural studies and the role of transcytotic vesicles. *J. Cereb. Blood Flow Metab.* **37**, 456–470, https://doi.org/10.1177/0271678X16629976

86 Castejon, O.J. (1984) Increased vesicular and vacuolar transport in traumatic human brain edema. A combined electron microscopic study and theoretical approach. *J. Submicrosc. Cytol.* **16**, 359–369

87 Nag, S., Manias, J.L. and Stewart, D.J. (2009) Expression of endothelial phosphorylated caveolin-1 is increased in brain injury. *Neuropathol. Appl. Neurobiol.* **35**, 417–426, https://doi.org/10.1111/j.1365-2990.2008.01009.x

88 Nag, S., Venugopalan, R. and Stewart, D.J. (2007) Increased caveolin-1 expression precedes decreased expression of occludin and claudin-5 during blood-brain barrier breakdown. *Acta Neuropathol.* **114**, 459–469, https://doi.org/10.1007/s00401-007-0274-x

89 Bucci, M., Gratton, J.P., Rudic, R.D., Acevedo, L., Roviezzo, F., Cirino, G. et al. (2000) *In vivo* delivery of the caveolin-1 scaffolding domain inhibits nitric oxide synthesis and reduces inflammation. *Nat. Med.* **6**, 1362–1367, https://doi.org/10.1038/82176

90 Minshall, R.D., Sessa, W.C., Stan, R.V., Anderson, R.G. and Malik, A.B. (2003) Caveolin regulation of endothelial function. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **285**, L1179–L1183, https://doi.org/10.1152/ajplung.00242.2003

91 McCaffrey, G., Staatz, W.D., Quigley, C.A., Nametz, N., Seelbach, M.J., Campos, C.R. et al. (2007) Tight junctions contain oligomeric protein assembly critical for maintaining blood-brain barrier integrity *in vivo*. *J. Neurochem.* **103**, 2540–2555

92 Jodoin, J., Demeule, M., Fenart, L., Cecchelli, R., Farmer, S., Linton, K.J. et al. (2003) P-glycoprotein in blood-brain barrier endothelial cells: interaction and oligomerization with caveolins. *J. Neurochem.* **87**, 1010–1023, https://doi.org/10.1046/j.1471-4159.2003.02081.x

93 Korn, A., Golan, H., Melamed, I., Pascual-Marqui, R. and Friedman, A. (2005) Focal cortical dysfunction and blood-brain barrier disruption in patients with Postconcussion syndrome. *J. Clin. Neurophysiol.* **22**, 1–9, https://doi.org/10.1097/01.WNP.0000150973.24324.A7

94 Tomkins, O., Shelef, I., Kaizerman, I., Eliushin, A., Afawi, Z., Misk, A. et al. (2008) Blood-brain barrier disruption in post-traumatic epilepsy. *J. Neurol. Neurosurg. Psychiatry* **79**, 774–777, https://doi.org/10.1136/jnnp.2007.126425

95 Glushakova, O.Y., Johnson, D. and Hayes, R.L. (2014) Delayed increases in microvascular pathology after experimental traumatic brain injury are associated with prolonged inflammation, blood-brain barrier disruption, and progressive white matter damage. *J. Neurotrauma* **31**, 1180–1193, https://doi.org/10.1089/neu.2013.3080

96 Badaut, J. and Bix, G.J. (2014) Vascular neural network phenotypic transformation after traumatic injury: potential role in long-term sequelae. *Transl. Stroke Res.* **5**, 394–406, https://doi.org/10.1007/s12975-013-0304-z

97 McCaffrey, G., Staatz, W.D., Sanchez-Covarrubias, L., Finch, J.D., Demarco, K., Laracuente, M.L. et al. (2012) P-glycoprotein trafficking at the blood-brain barrier altered by peripheral inflammatory hyperalgesia. *J. Neurochem.* **122**, 962–975, https://doi.org/10.1111/j.1471-4159.2012.07831.x

98 Marchi, N., Granata, T., Ghosh, C. and Janigro, D. (2012) Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. *Epilepsia* **53**, 1877–1886, https://doi.org/10.1111/j.1528-1167.2012.03637.x

99 Friedman, A. (2011) Blood-brain barrier dysfunction, status epilepticus, seizures, and epilepsy: a puzzle of a chicken and egg? *Epilepsia* **52**, 19–20, https://doi.org/10.1111/j.1528-1167.2011.03227.x

100 Farrell, J.S., Colangeli, R., Wolff, M.D., Wall, A.K., Phillips, T.J., George, A. et al. (2017) Postictal hypoperfusion/hypoxia provides the foundation for a unified theory of seizure-induced brain abnormalities and behavioral dysfunction. *Epilepsia*, https://doi.org/10.1111/epi.13827

101 Kovac, A., Erickson, M.A. and Banks, W.A. (2011) Brain microvascular pericytes are immunoactive in culture: cytokine, chemokine, nitric oxide, and LRP-1 expression in response to lipopolysaccharide. *J. Neuroinflammation* **8**, 139, https://doi.org/10.1186/1742-2094-8-139

102 Garbelli, R., de Bock, F., Medici, V., Rousset, M.C., Villani, F., Boussadia, B. et al. (2015) PDGFRβ(+) cells in human and experimental neuro-vascular dysplasia and seizures. *Neuroscience* **306**, 18–27, https://doi.org/10.1016/j.neuroscience.2015.07.090

103 Bar-Klein, G., Lublinsky, S., Kamintsky, L., Noyman, I., Veksler, R., Dalipaj, H. et al. (2017) Imaging blood-brain barrier dysfunction as a biomarker for epileptogenesis. *Brain J. Neurol.* **140**, 1692–1705, https://doi.org/10.1093/brain/awx073

104 van Vliet, E.A., Otte, W.M., Wadman, W.J., Aronica, E., Kooij, G., de Vries, H.E. et al. (2016) Blood-brain barrier leakage after status epilepticus in rapamycin-treated rats I: magnetic resonance imaging. *Epilepsia* **57**, 59–69, https://doi.org/10.1111/epi.13246

105 Dahm, R. (2006) Alzheimer's discovery. *Curr. Biol.* **16**, R906–R910, https://doi.org/10.1016/j.cub.2006.09.056

106 Serrano-Pozo, A., Frosch, M.P., Masliah, E. and Hyman, B.T. (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* **1**, a006189, https://doi.org/10.1101/cshperspect.a006189

107 Heppner, F.L., Ransohoff, R.M. and Becher, B. (2015) Immune attack: the role of inflammation in Alzheimer disease. *Nat. Rev. Neurosci.* **16**, 358–372, https://doi.org/10.1038/nrn3880

108 de la Torre, J.C. (2004) Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol.* **3**, 184–190, https://doi.org/10.1016/S1474-4422(04)00683-0

109 Itagaki, S., McGeer, P.L., Akiyama, H., Zhu, S. and Selkoe, D. (1989) Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *J. Neuroimmunol.* **24**, 173–182, https://doi.org/10.1016/0165-5728(89)90115-X

110 de la Torre, J.C. (2014) In-house heart-brain clinics to reduce Alzheimer's disease incidence. *J. Alzheimers Dis.* **42** (Suppl. 4), S431–S442

111 Gottesman, R.F., Schneider, A.L.C., Zhou, Y., Coresh, J., Green, E., Gupta, N. et al. (2017) Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA* **317**, 1443–1450, https://doi.org/10.1001/jama.2017.3090

112 Montagne, A., Nation, D.A., Pa, J., Sweeney, M.D., Toga, A.W. and Zlokovic, B.V. (2016) Brain imaging of neurovascular dysfunction in Alzheimer's disease. *Acta Neuropathol.* **131**, 687–707, https://doi.org/10.1007/s00401-016-1570-0

113 Scheltens, P., Blennow, K., Breteler, M.M.B., de Strooper, B., Frisoni, G.B., Salloway, S. et al. (2016) Alzheimer's disease. *Lancet* **388**, 505–517, https://doi.org/10.1016/S0140-6736(15)01124-1

114 Kisler, K., Nelson, A.R., Rege, S.V., Ramanathan, A., Wang, Y., Ahuja, A. et al. (2017) Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. *Nat. Neurosci.* **20**, 406–416, https://doi.org/10.1038/nn.4489

115 Roher, A.E., Esh, C., Kokjohn, T.A., Kalback, W., Luehrs, D.C., Seward, J.D. et al. (2003) Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler. Thromb. Vasc. Biol.* **23**, 2055–2062, https://doi.org/10.1161/01.ATV.0000095973.42032.44

116 Gabin, J.M., Tambs, K., Saltvedt, I., Sund, E. and Holmen, J. (2017) Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: the HUNT Study. *Alzheimers Res. Ther.* **9**, 37, https://doi.org/10.1186/s13195-017-0262-x

117 de Matos, A.M., de Macedo, M.P. and Rauter, A.P. (2017) Bridging type 2 diabetes and Alzheimer's disease: assembling the puzzle pieces in the quest for the molecules with therapeutic and preventive potential. *Med. Res. Rev.*, https://doi.org/10.1002/med.21440

118 Hays, C.C., Zlatar, Z.Z. and Wierenga, C.E. (2016) The utility of cerebral blood flow as a biomarker of preclinical Alzheimer's disease. *Cell. Mol. Neurobiol.* **36**, 167–179, https://doi.org/10.1007/s10571-015-0261-z

119 Iturria-Medina, Y., Sotero, R.C., Toussaint, P.J., Mateos-Pérez, J.M., Evans, A.C., Initiative, T.A.D.N. et al. (2016) Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat. Commun.* **7**, https://doi.org/10.1038/ncomms11934

120 Sagare, A.P., Bell, R.D., Zhao, Z., Ma, Q., Winkler, E.A., Ramanathan, A. et al. (2013) Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat. Commun.* **4**, 2932, https://doi.org/10.1038/ncomms3932

121 Bell, R.D., Winkler, E.A., Sagare, A.P., Singh, I., LaRue, B., Deane, R. et al. (2010) Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron* **68**, 409–427, https://doi.org/10.1016/j.neuron.2010.09.043

122 Fernández-Klett, F., Offenhauser, N., Dirnagl, U., Priller, J. and Lindauer, U. (2010) Pericytes in capillaries are contractile *in vivo*, but arterioles mediate functional hyperemia in the mouse brain. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 22290–22295, https://doi.org/10.1073/pnas.1011321108

123 Iliff, J.J., Wang, M., Liao, Y., Plogg, B.A., Peng, W., Gundersen, G.A. et al. (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci. Transl. Med.* **4**, 147ra111, https://doi.org/10.1126/scitranslmed.3003748

124 Nahirney, P.C., Reeson, P. and Brown, C.E. (2016) Ultrastructural analysis of blood-brain barrier breakdown in the peri-infarct zone in young adult and aged mice. *J. Cereb. Blood Flow Metab.* **36**, 413–425, https://doi.org/10.1177/0271678X15608396

125 Mandrekar-Colucci, S. and Landreth, G.E. (2010) Microglia and inflammation in Alzheimer's disease. *CNS Neurol. Disord. Drug Targets* **9**, 156–167, https://doi.org/10.2174/187152710791012071

126 Thériault, P., ElAli, A. and Rivest, S. (2015) The dynamics of monocytes and microglia in Alzheimer's disease. *Alzheimers Res. Ther.* **7**, 41, https://doi.org/10.1186/s13195-015-0125-2

127 Lai, A.Y. and McLaurin, J. (2012) Clearance of amyloid-β peptides by microglia and macrophages: the issue of what, when and where. *Future Neurol.* **7**, 165–176, https://doi.org/10.2217/fnl.12.6

128 Yin, Z., Raj, D., Saiepour, N., Van Dam, D., Brouwer, N. et al. (2017) Immune hyperreactivity of Aβ plaque-associated microglia in Alzheimer's disease. *Neurobiol. Aging* **55**, 115–122, https://doi.org/10.1016/j.neurobiolaging.2017.03.021

129 Landel, V., Baranger, K., Virard, I., Loriod, B., Khrestchatisky, M., Rivera, S. et al. (2014) Temporal gene profiling of the 5XFAD transgenic mouse model highlights the importance of microglial activation in Alzheimer's disease. *Mol. Neurodegener.* **9**, 33, https://doi.org/10.1186/1750-1326-9-33

130 Serrano-Pozo, A., Gómez-Isla, T., Growdon, J.H., Frosch, M.P. and Hyman, B.T. (2013) A phenotypic change but not proliferation underlies glial responses in Alzheimer disease. *Am. J. Pathol.* **182**, 2332–2344, https://doi.org/10.1016/j.ajpath.2013.02.031

131 Liddelow, S.A., Guttenplan, K.A., Clarke, L.E., Bennett, F.C., Bohlen, C.J., Schirmer, L. et al. (2017 26) Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **541**, 481–487, https://doi.org/10.1038/nature21029
132 Ulland, T.K., Song, W.M., Huang, S.C.-C., Ulrich, J.D., Sergushichev, A., Beatty, W.L. et al. (2017) TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell* **170**, 649–663.e13, https://doi.org/10.1016/j.cell.2017.07.023
133 Ulrich, J.D., Ulland, T.K., Colonna, M. and Holtzman, D.M. (2017) Elucidating the role of TREM2 in Alzheimer's disease. *Neuron* **94**, 237–248, https://doi.org/10.1016/j.neuron.2017.02.042
134 Sims, R., van der Lee, S.J., Naj, A.C., Bellenguez, C., Badarinarayan, N., Jakobsdottir, J. et al. (2017) Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat. Genet.*, https://doi.org/10.1038/ng.3916
135 Bell, R.D., Winkler, E.A., Singh, I., Sagare, A.P., Deane, R., Wu, Z. et al. (2012) Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature* **485**, 512–516
136 Bu, G., Liu, C.-C. and Kanekiyo, T. (2013) Vascular hypothesis of Alzheimer's disease: role of apoE and apoE receptors. *Mol. Neurodegener.* **8** (Suppl. 1), 020
137 Ramanathan, A., Nelson, A.R., Sagare, A.P. and Zlokovic, B.V. (2015) Impaired vascular-mediated clearance of brain amyloid beta in Alzheimer's disease: the role, regulation and restoration of LRP1. *Front. Aging Neurosci.* **7**, 136, https://doi.org/10.3389/fnagi.2015.00136
138 Nishitsuji, K., Hosono, T., Nakamura, T., Bu, G. and Michikawa, M. (2011) Apolipoprotein E regulates the integrity of tight junctions in an isoform-dependent manner in an *in vitro* blood-brain barrier model. *J. Biol. Chem.* **286**, 17536–17542, https://doi.org/10.1074/jbc.M111.225532
139 Lan, Y.-L., Chen, J.-J., Hu, G., Xu, J., Xiao, M. and Li, S. (2017) Aquaporin 4 in astrocytes is a target for therapy in Alzheimer's disease. *Curr. Pharm. Des.*
140 Vinters, H.V. (1987) Cerebral amyloid angiopathy. A critical review. *Stroke* **18**, 311–324, https://doi.org/10.1161/01.STR.18.2.311
141 Poduslo, J.F., Hultman, K.L., Curran, G.L., Preboske, G.M., Chamberlain, R., Marjańska, M. et al. (2011) Targeting vascular amyloid in arterioles of Alzheimer disease transgenic mice with amyloid beta protein antibody-coated nanoparticles. *J. Neuropathol. Exp. Neurol.* **70**, 653–661, https://doi.org/10.1097/NEN.0b013e318225038c
142 Fisher, M., Vasilevko, V. and Cribbs, D.H. (2012) Mixed cerebrovascular disease and the future of stroke prevention. *Transl. Stroke Res.* **3**, 39–51, https://doi.org/10.1007/s12975-012-0185-6
143 Reijmer, Y.D., van Veluw, S.J. and Greenberg, S.M. (2016) Ischemic brain injury in cerebral amyloid angiopathy. *J. Cereb. Blood Flow Metab.* **36**, 40–54, https://doi.org/10.1038/jcbfm.2015.88
144 Abbott, N.J. (2004) Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. *Neurochem. Int.* **45**, 545–552, https://doi.org/10.1016/j.neuint.2003.11.006
145 Kimbrough, I.F., Robel, S., Roberson, E.D. and Sontheimer, H. (2015) Vascular amyloidosis impairs the gliovascular unit in a mouse model of Alzheimer's disease. *Brain J. Neurol.* **138**, 3716–3733, https://doi.org/10.1093/brain/awv327
146 Wojtas, A.M., Kang, S.S., Olley, B.M., Gatherer, M., Shinohara, M., Lozano, P.A. et al. (2017) Loss of clusterin shifts amyloid deposition to the cerebrovasculature via disruption of perivascular drainage pathways. *Proc. Natl. Acad. Sci. U.S.A.* **114**, E6962–E6971, https://doi.org/10.1073/pnas.1701137114
147 Sutcliffe, J.G., Hedlund, P.B., Thomas, E.A., Bloom, F.E. and Hilbush, B.S. (2011) Peripheral reduction of β-amyloid is sufficient to reduce brain β-amyloid: implications for Alzheimer's disease. *J. Neurosci. Res.* **89**, 808–814, https://doi.org/10.1002/jnr.22603
148 Vriens, E.M., Kraaier, V., Musbach, M., Wieneke, G.H. and van Huffelen, A.C. (1989) Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. *Ultrasound Med. Biol.* **15**, 1–8, https://doi.org/10.1016/0301-5629(89)90125-7
149 Krejza, J., Mariak, Z., Walecki, J., Szydlik, P., Lewko, J. and Ustymowicz, A. (1999) Transcranial color Doppler sonography of basal cerebral arteries in 182 healthy subjects: age and sex variability and normal reference values for blood flow parameters. *AJR Am. J. Roentgenol.* **172**, 213–218, https://doi.org/10.2214/ajr.172.1.9888770
150 Reich, T. and Rusinek, H. (1989) Cerebral cortical and white matter reactivity to carbon dioxide. *Stroke* **20**, 453–457, https://doi.org/10.1161/01.STR.20.4.453
151 Farkas, E. and Luiten, P.G. (2001) Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog. Neurobiol.* **64**, 575–611, https://doi.org/10.1016/S0301-0082(00)00068-X
152 Sonntag, W.E., Lynch, C.D., Cooney, P.T. and Hutchins, P.M. (1997) Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1. *Endocrinology* **138**, 3515–3520, https://doi.org/10.1210/endo.138.8.5330
153 Riddle, D.R., Sonntag, W.E. and Lichtenwalner, R.J. (2003) Microvascular plasticity in aging. *Ageing Res. Rev.* **2**, 149–168, https://doi.org/10.1016/S1568-1637(02)00064-8
154 Sonntag, W.E., Eckman, D.M., Ingraham, J. and Riddle, D.R. (2007) Regulation of cerebrovascular aging. In *Brain Aging: Models, Methods, and Mechanisms* (Riddle, D.R., ed.), CRC Press/Taylor & Francis, Boca Raton (FL), , http://www.ncbi.nlm.nih.gov/books/NBK3879/
155 Bell, M.A. and Ball, M.J. (1981) Morphometric comparison of hippocampal microvasculature in ageing and demented people: diameters and densities. *Acta Neuropathol.* **53**, 299–318, https://doi.org/10.1007/BF00690372
156 Brown, W.R. and Thore, C.R. (2011) Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol. Appl. Neurobiol.* **37**, 56–74, https://doi.org/10.1111/j.1365-2990.2010.01139.x
157 Yang, T., Sun, Y., Lu, Z., Leak, R.K. and Zhang, F. (2017) The impact of cerebrovascular aging on vascular cognitive impairment and dementia. *Ageing Res. Rev.* **34**, 15–29, https://doi.org/10.1016/j.arr.2016.09.007
158 Buée, L., Hof, P.R., Bouras, C., Delacourte, A., Perl, D.P., Morrison, J.H. et al. (1994) Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders. *Acta Neuropathol.* **87**, 469–480, https://doi.org/10.1007/BF00294173

159 Bullitt, E., Zeng, D., Mortamet, B., Ghosh, A., Aylward, S.R., Lin, W. et al. (2010) The effects of healthy aging on intracerebral blood vessels visualized by magnetic resonance angiography. *Neurobiol. Aging* **31**, 290–300, https://doi.org/10.1016/j.neurobiolaging.2008.03.022
160 Simpson, J.E., Wharton, S.B., Cooper, J., Gelsthorpe, C., Baxter, L., Forster, G. et al. (2010) Alterations of the blood-brain barrier in cerebral white matter lesions in the ageing brain. *Neurosci. Lett.* **486**, 246–251, https://doi.org/10.1016/j.neulet.2010.09.063
161 Montagne, A., Barnes, S.R., Sweeney, M.D., Halliday, M.R., Sagare, A.P., Zhao, Z. et al. (2015) Blood-brain barrier breakdown in the aging human hippocampus. *Neuron* **85**, 296–302, https://doi.org/10.1016/j.neuron.2014.12.032
162 Fernández-Klett, F. and Priller, J. (2015) Diverse functions of pericytes in cerebral blood flow regulation and ischemia. *J. Cereb. Blood Flow Metab.* **35**, 883–887, https://doi.org/10.1038/jcbfm.2015.60
163 Hall, C.N., Reynell, C., Gesslein, B., Hamilton, N.B., Mishra, A., Sutherland, B.A. et al. (2014) Capillary pericytes regulate cerebral blood flow in health and disease. *Nature* **508**, 55–60, https://doi.org/10.1038/nature13165
164 Pieper, C., Pieloch, P. and Galla, H.-J. (2013) Pericytes support neutrophil transmigration via interleukin-8 across a porcine co-culture model of the blood-brain barrier. *Brain Res.* **1524**, 1–11, https://doi.org/10.1016/j.brainres.2013.05.047
165 Welser-Alves, J.V., Boroujerdi, A., Tigges, U. and Milner, R. (2014) Analysis of TNF-alpha-mediated cerebral pericyte remodeling. *Methods Mol. Biol.* **1155**, 81–93, https://doi.org/10.1007/978-1-4939-0669-7_8
166 Jansson, D., Scotter, E.L., Rustenhoven, J., Coppieters, N., Smyth, L.C.D., Oldfield, R.L. et al. (2016) Interferon-γ blocks signalling through PDGFRβ in human brain pericytes. *J. Neuroinflammation* **13**, 249, https://doi.org/10.1186/s12974-016-0722-4
167 Minghetti, L. (2004) Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases. *J. Neuropathol. Exp. Neurol.* **63**, 901–910, https://doi.org/10.1093/jnen/63.9.901
168 Zhao, M.L., Liu, J.S., He, D., Dickson, D.W. and Lee, S.C. (1998) Inducible nitric oxide synthase expression is selectively induced in astrocytes isolated from adult human brain. *Brain Res.* **813**, 402–405, https://doi.org/10.1016/S0006-8993(98)01023-3
169 Jansson, D., Rustenhoven, J., Feng, S., Hurley, D., Oldfield, R.L., Bergin, P.S. et al. (2014) A role for human brain pericytes in neuroinflammation. *J. Neuroinflammation* **11**, 104, https://doi.org/10.1186/1742-2094-11-104
170 Sagare, A.P., Sweeney, M.D., Makshanoff, J. and Zlokovic, B.V. (2015) Shedding of soluble platelet-derived growth factor receptor-β from human brain pericytes. *Neurosci. Lett.* **607**, 97–101, https://doi.org/10.1016/j.neulet.2015.09.025