

Review

Cellular and molecular mechanisms in vascular repair after traumatic brain injury: a narrative review

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Abstract

Traumatic brain injury (TBI) disrupts normal brain function and is associated with high morbidity and fatality rates. TBI is characterized as mild, moderate or severe depending on its severity. The damage may be transient and limited to the dura matter, with only subtle changes in cerebral parenchyma, or life-threatening with obvious focal contusions, hematomas and edema. Blood vessels are often injured in TBI. Even in mild TBI, dysfunctional cerebral vascular repair may result in prolonged symptoms and poor outcomes. Various distinct types of cells participate in vascular repair after TBI. A better understanding of the cellular response and function in vascular repair can facilitate the development of new therapeutic strategies. In this review, we analyzed the mechanism of cerebrovascular impairment and the repercussions following various forms of TBI. We then discussed the role of distinct cell types in the repair of meningeal and parenchyma vasculature following TBI, including endothelial cells, endothelial progenitor cells, pericytes, glial cells (astrocytes and microglia), neurons, myeloid cells (macrophages and monocytes) and meningeal lymphatic endothelial cells. Finally, possible treatment techniques targeting these unique cell types for vascular repair after TBI are discussed.

Key words: Traumatic brain injury, Angiogenesis, Vascular repair

Highlights

- Cerebrovascular impairment is an important hallmark of traumatic brain injury.
- The consequences of cerebrovascular impairment after TBI are discussed.
- Various cell types contribute to vascular repair post-TBI.

Background

Traumatic brain injury (TBI) is caused by a bump, the brain's movement in response to acceleration/deceleration accidents or a penetrating injury (such as a gunshot) to the head that disrupts brain function. People of all ages can be affected by TBI. The population most susceptible to TBI includes older adults, ethnic minorities, service members in the military and veterans, homeless people living in detention and correctional facilities or rural areas, and victims of domestic violence [1–4].

TBI causes primary vascular damage due to mechanical forces. Depending on the severity, location and injury frequency, blood vessel impairment may be limited to dura mater, with only transient symptoms, or may result in obvious tissue contusions, hematoma and subsequent brain damage involving the brain parenchyma, resulting in long-term repercussions. Vascular repair is important for the recovery of dural tissue, restoration of meningeal immune homeostasis [5] and the prevention of delayed hypoperfusion, edema, hemorrhage and other secondary injuries involving the parenchyma [6, 7]. TBI may induce chronic neurodegenerative changes due to the impairment of microvasculature [8]. Defective repair of cerebral vasculature may exacerbate brain injury symptom persistence and lead to poor outcomes.

Review

Classification of TBI

TBI is categorized based on the mechanism (closed *vs* open; impact *vs* blast), whereas clinical severity is based on the Glasgow coma scale, location (diffuse *vs* focal) and symptoms (post-concussive *vs* sub-concussive) [9, 10]. Traditionally, TBI has been classified as mild, moderate and severe based on severity. Different types of TBI share common pathophysiological changes induced by the primary injury. However, distinct cellular responses are observed due to varying degrees and mechanisms of injury.

The most common type of TBI is mild (mTBI). Most mTBIs occur in individuals >75 years old [11]. mTBI is typically induced by a knock or jolt to the head, with no discernible brain parenchymal abnormalities. The majority of head injury outcomes, such as skull fractures, structural abnormalities and hemorrhage, are undetected in routine magnetic resonance imaging (MRI) and computerized tomography (CT) scans [12]. Clinical and pre-clinical studies suggest that 7–33% of patients diagnosed with mTBI experience long-term and progressive cognitive impairment, despite the generally transient nature of the symptoms induced by mTBI [13].

A blow, bump or penetrating injury to the dura mater and cerebral parenchyma can induce moderate or severe TBI, which can have devastating long-term health effects. Macroscopic injuries to the cerebral parenchyma include shearing of white matter tracts, hematomas (intracerebral and extracerebral), focal contusions and diffuse swelling. Microscopic injuries to the cerebral parenchyma include

microporation of membranes, leaky ion channels and abnormal steric conformation of proteins inside the cells [14]. After the initial brain injury, secondary impairments such as calcium-mediated damage, free-radical production, inflammation, mitochondrial dysfunction and gene activation occur within hours or days. Direct structural damage of brain tissue and vasculature by primary injury is untreatable. Efforts should be made to limit the external impact by wearing a helmet and preventing head acceleration by immobilizing the head [9, 15]. In the case of moderate and severe TBIs, it is vital to reduce the deleterious effects of secondary injury, which can cause persistent symptoms. An impaired cerebral vasculature contributes significantly to both initial and subsequent damage following TBI.

Cerebral vascular impairment after TBI

The primary injury produced by the mechanical forces of TBI may directly affect meningeal and parenchymal blood vessels. Cerebrovascular dysfunction plays a role in the etiology of all types of TBI and is a significant feature of TBI. Structural abnormalities of cerebral vasculature after TBI include vacuolation, degeneration, discontinuity and necrosis of pericytes. Primary mechanical damage to the vessel walls accompanied by irreversible neuronal impairment can be observed early after the injury via ultrastructural analysis [16]. Changes in endothelial cells (ECs) can be seen in the acute phase of TBI by electron microscopy (EM) as early as 3 hours after TBI and up to at least a week [17]. EM images of the membrane reveal thickening, rarefaction, matrix disorder with reduplication and bifurcation, and basement membrane vacuolization. After a TBI, the cerebral vasculature undergoes ultrastructural alterations in the subacute stage (7–30 days later), including fibrous changes in the arterial wall, apoptotic ECs, internal elastic lamina corrugation, extracellular matrix degradation, condensed nuclei and heterophagy [18]. Technologies for the detection of cerebral vascular impairment after TBI in experimental models and clinical applications include functional MRI, laser Doppler flowmetry, *in vivo* microscopy, transcranial Doppler, CT and subtraction angiography, which are discussed thoroughly in other comprehensive reviews [18, 19].

Vascular impairment within the meninges Meninges, including dura mater, arachnoid mater and pia mater, surround the brain. The tough leathery membrane called the dura mater lies on the outside and is vulnerable due to its perforated blood arteries and lack of tight junctions. Leptomeninges are composed of arachnoid and pia maters [20]. The meninges represent a highly vascularized physical barrier involved in the immune surveillance of the brain [21]. Meningeal injury can be observed in more than half of all patients with mTBI [22]. The TBI model also reveals a significant decrease in microvascular density within the area of brain contusion accompanied by an obvious inflammatory response [22, 23]. Persistent symptoms such as fatigue, headache, impaired

concentration and memory, anxiety and irritability may result from inadequate meningeal vascular repair following mTBI [24].

Secondary injury following cerebral vascular impairment

Hemorrhage and coagulopathy Nearly half of TBI patients experience hemorrhage, especially those with moderate and severe TBI [25, 26]. TBI can induce epidural, subdural, subarachnoid and parenchymal hemorrhages. Epidural hematomas develop between the dura mater and the inner lining of the skull. After a TBI, subdural hematomas form between the arachnoid and dura mater and are associated with poor prognosis [27]. Poor outcomes and higher mortality are linked to subarachnoid hemorrhage, which occurs between the pia and arachnoid mater [28]. Hemorrhage after TBI results in the accumulation of hemosiderin/ferritin, which is believed to be neurotoxic [29]. White matter impairment is reportedly associated with microbleeds following TBI [30]. Coagulopathy is associated with higher mortality and poor outcomes following TBI, with an incidence of 33% [31]. The mechanism of coagulopathy following TBI includes the release of tissue factors into the blood, coagulation factor depletion, platelet reduction, blood–brain barrier (BBB) disruption and an increase in circulating microparticles [32, 33]. A low platelet count increases the likelihood of hemorrhage [34].

BBB dysfunction and edema The BBB, composed of ECs, astrocytes and pericytes, maintains the brain's extremely limited environment and prohibits the free entry of circulating immune cells and blood-borne factors into the central nervous system (CNS) [35, 36]. BBB disruption occurs within hours following TBI [37, 38] and is associated with increased morbidity and mortality [39]. TBI disrupts the tight junction proteins connecting endothelial cells and sealing the BBB [40], followed by infiltration of immune cells and molecules such as neutrophils and albumin, aggravating the inflammatory response, edema and hypertension [41, 42]. In a study of individuals with severe non-penetrating TBI, a breach of the BBB was identified in 44% of patients and was associated with poor long-term consequences [43]. After a TBI, the altered BBB often recovers to normal within a few weeks. In some situations of mTBI, BBB dysfunction might linger for months or years. [44, 45].

Cerebral edema develops at the site of a TBI and eventually fuses with the surrounding tissue, resulting in death in 50% of all cases following severe TBI [46]. Cerebral edema is classified into vasogenic and cytotoxic types. After TBI, blood vessel components leak into the brain parenchyma, creating an osmotic gradient that induces water migration from the blood vessels into the extracellular space, resulting in vasogenic edema [47]. Vasogenic edema is characterized by tissue swelling, compression of brain structure, high intracranial pressure and altered blood flow [48]. Vasogenic edema occurs within the first few hours post-TBI. Cytotoxic edema occurs within a few days of the damage and can last up to 2 weeks

[49, 50]. Cytotoxic edema results from the storage of excess water inside the cell due to defective sodium and potassium pumps in the cell membrane [47]. In the mouse model of ischemic stroke, the inflow of cerebral spinal fluid (CSF) into ischemic tissue triggered by spreading depolarization also contributes to brain swelling. The glymphatic system is also intimately involved in this process. Several hours after CSF influx, Na^+ influx and edema in the endothelial cells of the brain are increased by the expression of sulfonylurea receptor-1-transient receptor potential cation channel subfamily M member 4 cation channels [51].

Changes in cerebral blood flow and ischemia Depending on the location, magnitude and type of lesion, both global and regional alterations in cerebral blood flow (CBF) are seen in TBI. CBF often decreases within 12 h after a TBI [52, 53]. Humans typically have a CBF of 45–50 ml/100 ml/min, which can plummet to 18–20 ml/100 ml/min in the acute phase following severe TBI [52, 54]. The decline in CBF implies that ischemia plays a significant role in secondary damage following TBI and, in many cases, shares comparable pathophysiological pathways with stroke. In addition, an increase in CBF may occur in patients after the acute phase of TBI [55, 56]. Several studies have indicated that TBI may lead to subsequent stroke [57–59]. In a patient cohort of TBI, a decrease in CBF and cerebral oxygen metabolism was observed after TBI by oxygen positron emission tomography [60]. In addition, TBI leads to tissue hypoxia not only within the regions with structural abnormalities but also in the regions without apparent macrovascular ischemia [61]. Significant decrease in brain tissue oxygen in ischemia after TBI may lead to malignant cerebral edema and poor outcomes [62]. The alterations in CBF following TBI may be attributed to impaired autoregulation of CBF, resulting in adverse outcomes [63–66]. Vasospasm is defined as aberrant constriction of blood vessels, which occurs in ~19–68% of patients with TBI [67], reducing CBF in wounded tissue and possibly inducing ischemic injury. Vasospasms are normally temporary; however, they can linger for 14 to 30 days in some cases of closed head traumas and blast injuries [68, 69]. Potential vasospasm causes include hypertension, subarachnoid hemorrhage and the production of endothelin-1 by pericytes following TBI [70, 71].

Cellular response and function in vascular repair after TBI

Depending on the severity of the injury, the repair of cerebral vasculature following TBI can last several weeks [72, 73]. The main mechanisms of vascular repair after TBI are angiogenesis and vasculogenesis, which contribute to the development of a primitive vasculature during the embryonic phase and promote vascular repair in adulthood following TBI. These intricate yet distinct processes play a crucial role in repairing the damaged vasculature following TBI [74, 75]. Angiogenesis is characterized by EC proliferation, migration, tube formation, branching and anastomosis [76]. Vascular

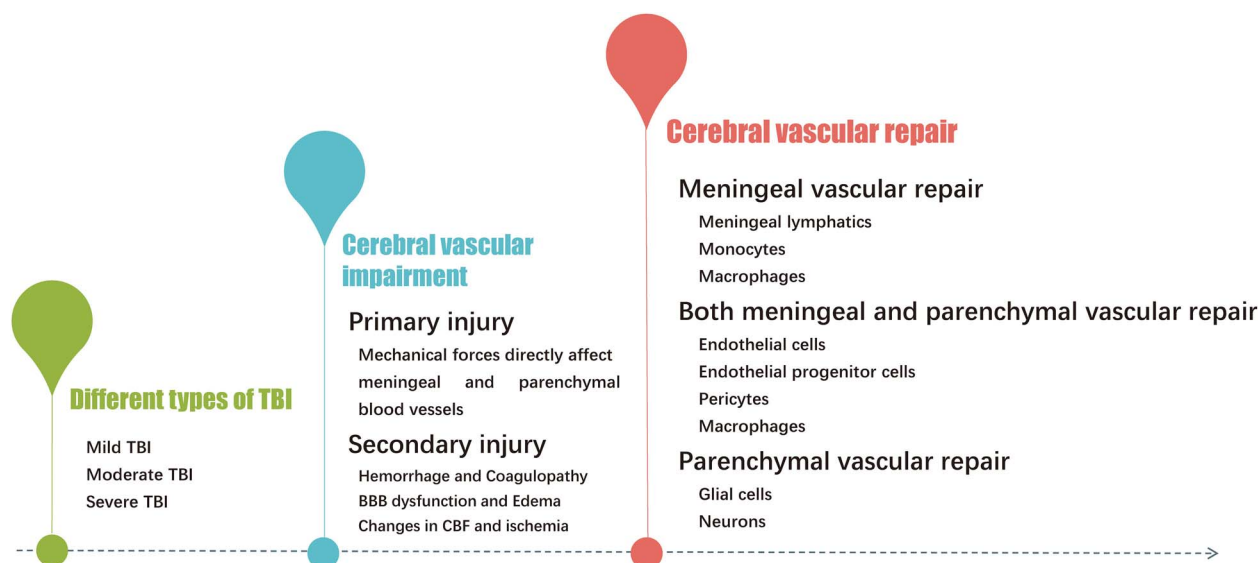


Figure 1. Schematic diagram showing an overview of cerebral vascular impairment and repair after traumatic brain injury (TBI). BBB blood–brain barrier, CBF cerebral blood flow

endothelial growth factor (VEGF), a soluble factor released by vascular cells and upregulated after TBI, mediates the proliferation of ECs from 12 h to 21 days after TBI [77, 78]. VEGF is a promising target for novel TBI therapeutic strategies due to its significant role in promoting angiogenesis [79, 80]. The proper organization of the vascular tree requires a balance between tubulogenesis, vascular branching, elongation and pruning. Imbalance in these processes leads to malformed and fragile vessels with dysregulated arteriovenous differentiation [81].

Rapid formation of new vasculature can be observed after TBI. Vascular repair is a complex process that involves many different types of cells. ECs, endothelial progenitor cells (EPCs), pericytes and macrophages participate in meningeal and parenchymal vascular repair after TBI. Meningeal lymphatic ECs and myeloid cells, including non-parenchymal macrophages and monocytes, play an important role in meningeal vascular repair. In moderate or severe TBI, glial cells (astrocytes and microglia) and neurons regulate parenchymal vascular repair. Schematic diagrams illustrating cerebral vascular impairment and cellular responses in vascular repair after TBI are presented in Figure 1 and 2.

ECs are essential components of blood vessels. The integrity and normal function of the BBB depend on tightly interconnected ECs. Injury to ECs may result in the production of inflammatory cytokines, oxidative stress, increased cellular adhesion molecules and vasogenic edema due to extravasation of plasma proteins [82–84]. The main mechanisms of vascular repair after TBI are angiogenesis and vasculogenesis. The first step of angiogenesis is vasodilation, which is regulated by nitric oxide. The permeability of vasculature increases in response to Src kinase and VEGF

via the formation of vesiculo–vacuolar organelles, fenestrations, and redistribution of vascular endothelial cadherin and platelet endothelial cell adhesion molecule-1 [85]. Plasma proteins extravasate following the increased permeability of vasculature and form a transient migratory scaffold for ECs. Proteinases, including matrix metalloproteinase (MMP), heparinase or chymase, and plasminogen activator, mediate angiogenesis by releasing or activating growth factors, such as basic fibroblast growth factor (bFGF), VEGF and insulin-like growth factor-1 (IGF-1) secreted within the extracellular matrix, and by degrading the matrix itself [86]. VEGF drives the differentiation of ECs into distinct subtypes to restore nutrient supply and oxygenation by attracting new vessel sprouts [87]. In addition, ECs in dura mater exhibit intrinsic angiogenic potential via VEGF receptor 2 (VEGFR2) signaling [5].

After clearing the obstacles on the passage for ECs migration, proliferating ECs travel to distant locations. ECs frequently form solid cords before acquiring a lumen. Interactions between tip cells, stalk cells and phalangeal cells promote capillary sprouting. During capillary sprouting, the three subtypes of ECs play a highly specific role [88]. Tip cells are non-proliferative and highly migratory ECs that guide the new sprout in the right direction. Stalk cells exhibit a high proliferative capacity and elongate the new sprout. The highly mature area of the vessel is marked by quiescent phalangeal cells with their cobblestone shape [89]. Neighboring ECs are connected by tight junctions (TJs), adherens junctions and gap junctions. The proteins at endothelial junctions are remodeled dynamically under physiological and pathological conditions [90]. TJs are composed of claudins, occludin and junctional adhesion molecules [91]. Junctional proteins

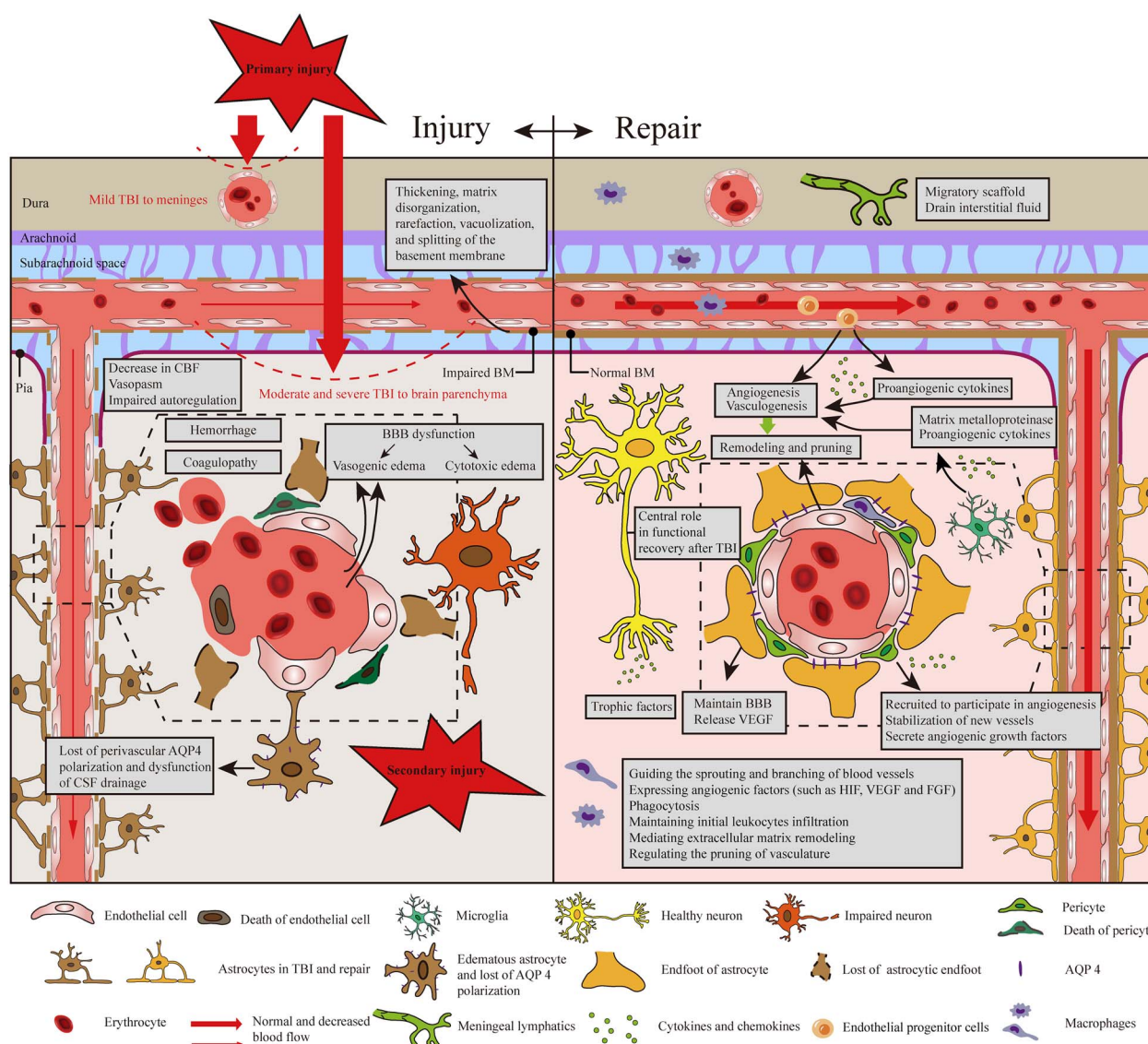


Figure 2. Schematic diagram of cerebral vascular impairment and cellular responses in vascular repair after traumatic brain injury (TBI). Primary injuries due to mechanical forces directly damage blood vessels after TBI. Structural abnormalities of cerebral vasculature after TBI include vacuolation, degeneration, discontinuity and necrosis of pericytes. Thickening, rarefaction, matrix disorder with reduplication and bifurcation, and basement membrane vacuolization can be observed after TBI. Aside from the predominant injury within the meninges in mTBI, secondary injuries, including hemorrhage, coagulopathy, BBB dysfunction, edema, reduced cerebral blood flow (CBF) and ischemia adversely affect brain parenchyma in moderate-to-severe TBI. Hemorrhage can progress gradually and result in vasospasms, intracranial hypertension and compression of brain tissue. The release of tissue factors into the blood, coagulation-factor depletion, platelet reduction, BBB disruption and increased circulating microparticles may lead to coagulopathy. BBB disruption occurs within hours following TBI, aggravating the inflammatory response and cerebral edema. Cerebral edema is classified into vasogenic and cytotoxic types. Vasogenic edema results from the leakage of blood-vessel components into the brain parenchyma, creating an osmotic gradient that induces water migration from the blood vessels into the extracellular space. Cytotoxic edema results from the storage of excess water inside the cell due to defective sodium and potassium pumps in the cell membrane. Both global and regional alterations in CBF are seen in TBI. The alterations in CBF following TBI may be attributed to impaired autoregulation of CBF and vasospasm. The decline in CBF may further lead to ischemic stroke and malignant cerebral edema. Distinct types of cells are involved in the process of vascular repair. Endothelial cells, endothelial progenitor cells, pericytes and macrophages participate in meningeal and parenchymal vascular repair after TBI. Meningeal lymphatic endothelial cells and non-parenchymal macrophages play an important role in meningeal vascular repair. Astrocytes, microglia and neurons mainly regulate parenchymal vascular repair in moderate or severe TBI. *AQP4* aquaporin 4, *VEGF* vascular endothelial growth factor, *HIF* hypoxia-inducible factor, *FGF* fibroblast growth factor, *CSF* cerebral spinal fluid, *BBB* blood-brain barrier, *BM* basement membrane

interact with the actin cytoskeleton dynamically and regulate the permeability of ECs [92]. Disruption of TJs is associated with leakage of BBB and edema in the brain after TBI [35, 90, 93].

Both remodeling and 'pruning' occur during the maturation of the endothelial network, forming a network of

branched vessels [94]. The levels of MMP-9 are increased in the hypoxic angiogenic and post-hypoxic vascular pruning response during cerebrovascular remodeling under chronic mild hypoxia [95]. Pruning is designed to establish an efficient, mature vasculature [96–99]. Apoptosis of ECs was observed during vascular pruning in zebrafish

internal carotid artery [100] and mouse retinal blood vessels [101]. Macrophages play a critical role in vascular pruning by regulating the apoptosis of ECs during the regression of hyaloid blood vessels in developing eyes [102].

EPCs The level of circulating EPCs was found to be associated with clinical severity and outcome in patients after TBI [103]. In patients with mTBI, the percentage of EPCs expressing C-X-C chemokine receptor type 4 at 7 days after TBI was found to be related to clinical outcome at 3 months. Changes in circulating EPCs were also found to be related to platelets and blood glucose levels [104, 105]. In a rat TBI model, CD34⁺ cells increased significantly in both peripheral circulation and brain tissue, with a close relation to angiogenesis after TBI [106]. EPCs in circulation are associated with hemangioblast stem cells and contribute to the development of postnatal vasculature via angiogenesis and vasculogenesis [107]. EPCs facilitate neovascularization *in vivo* via proliferation and differentiation into ECs. It has been shown that EPCs derived from peripheral blood mononuclear cells integrate into sites of myocardial neovascularization [108]. In patients with acute myocardial infarction, intracoronary infusion of bone marrow or peripheral blood-derived progenitors resulted in significant benefits in post-infarction remodeling [109, 110]. Statin treatment in a model of hindlimb ischemia led to an increase in circulating EPCs, angiogenic cytokines and angiogenesis [111]. An increase in new blood vessels and blood perfusion were observed after the mobilization of EPCs to promote the recovery of ischemic tissue [112, 113]. Increased numbers of circulating EPCs and angiogenesis were observed around the injured area after TBI. EPC transplantation or mobilization of circulating EPCs improves neurological outcomes after TBI by promoting angiogenesis [114–116]. Activation of Notch signaling was found to enhance the angiogenic ability of EPCs and promote vascular and tissue repair after mTBI [117]. In addition to neovascularization, EPCs promote the survival and proliferation of ECs by secreting various cytokines. EPCs are regulated by cytokines and growth factors released by injured tissues [118]. During angiogenesis in tumor or ischemic injury, the circulating level of VEGF increases [119–121], mobilizing EPCs from bone marrow. Conversely, Ang-1 inhibits the release of EPCs from bone marrow [122, 123].

Pericytes Pericytes play an important role in CBF regulation [124, 125], maintenance of BBB integrity [126, 127], formation of new blood vessels [128], scar formation [112] and transendothelial vesicle trafficking [126, 127]. Disruption of platelet-derived growth factor-B/PDGF receptor signaling after TBI results in the loss of pericyte–EC interaction and neurovascular dysfunction [35]. After TBI, pericytes are crucial for restoring the vasculature [129]. Pericytes line the exterior of cerebral blood vessels and are in direct contact with ECs [130]. Within hours of TBI in a rat model of controlled cortical impact, nearly 40% of pericytes relocated

to the injured basal lamina area [71]. The recruitment of pericytes is important for angiogenesis and stabilization of new vessels [131]. Reduced pericyte numbers were found in the early stages post-injury in a controlled cortical impact model [132].

To allow ECs to form vessel sprouts, pericytes must first detach from the vessel wall [71]. To separate pericytes from the vessels, several angiogenic factors are necessary, including the VEGF-A/VEGFR2 signal and the VEGF120 isoform [133, 134]. In the later stages of TBI, a process known as pericytosis—a dramatic increase in reactive pericytes racked up around the lesion—occurs. Angiogenic growth factors secreted by activated pericytes mediate EC activity and maintain blood-vessel integrity [130].

Macrophages Bone marrow-derived monocytes detect blood vessel damage during vascular injury and repair. They accumulate at the injury site due to the chemokine gradient. Vascular repair by macrophages occurs via the following mechanisms: (1) guiding the sprouting and branching of blood vessels for neovascularization by bridging tip cells directly; (2) enhancing smooth muscle cells and EC proliferation by angiogenic factors (FGF, VEGF and hypoxia-inducible factor); (3) necrotic cell debris and pathogen elimination by phagocytosis; (4) the release of pro-inflammatory chemokines and cytokines during initial leukocyte infiltration; (5) release of MMPs to mediate extracellular matrix remodeling; and (6) regulation of vascular pruning by pro-apoptotic factors [77, 102, 135–137].

Vascular repair is controlled by two types of activated macrophages: anti-angiogenic M1 macrophages during the inflammatory phase induced by damage-associated molecular patterns or pathogen-associated molecular patterns; and pro-angiogenic M2 macrophages (including the M2a and M2c subsets) at later stages [138]. M2 macrophages play a role in vascular repair after neutrophils and macrophages remove harmful stimuli [139]. Interleukin (IL)-4 induces M2a macrophages, which increase the expression of FGF2, IGF-1 and C-C motif chemokine ligand to promote angiogenesis. M2c is induced by IL-10 and mainly expresses the placental growth factor [140]. Meanwhile, M1 macrophages also produce pro-angiogenic factors, including VEGF and FGF2 [141]. The perivascular space contains tissue-resident macrophages that are in close proximity to the vessel walls [142]. Following weight drop injury, one study reported a substantial increase in CD163⁺ perivascular macrophages [143]. The antimicrobial reaction of myelomonocytic cells has been reported to impede vascular repair via interferon signaling [144].

Meningeal lymphatics and macrophages in meningeal vascular repair after mTBI Meningeal lymphatic ECs (mLECs) on the brain surface participate in CSF drainage and neuroimmune function [145–149]. Meningeal lymphatic vessels in mice regulate the amount of CSF and their loss is linked to cognitive impairments [150]. Edema was decreased by

improving the function of meningeal lymphatics after TBI [151]. Recent evidence suggests that meningeal lymphatics are modified after brain injury and may actively engage in brain tissue and vascular repair [152–154]. In a mouse model of TBI, dysfunctional meningeal lymphatic drainage was detected within hours and persisted for at least 1 month [153]. In a zebrafish model of cerebrovascular injury, the drastic ingrowth of meningeal lymphatics into the injured brain parenchyma was regulated by VEGF-C. Meningeal lymphatic repair of cerebrovascular damage appears to be mediated via drainage of interstitial fluid from the injured tissue via the lumenized ingrowth meningeal lymphatics and acting as “growing tracks” for nascent blood vessels. However, they promote the development of blood vasculature [155, 156].

A heterogeneous population of myeloid cells, including parenchymal microglia and non-parenchymal perivascular macrophages (PVMs), meningeal macrophages and choroid plexus macrophages populate the meninges in addition to mLECs [157–159]. Meningeal macrophages exhibit amoeboid morphology and movement. PVMs are long, highly oriented cells that extend and retract their protrusions along the blood vessel wall [160]. Non-parenchymal PVMs are important effectors and regulators at the CNS borders in many neurological diseases. The LEC marker hyaluronan receptor (LYVE)-1 is also expressed by non-parenchymal macrophages [161]. More than half of angiogenic and wound-localizing CD206⁺ macrophages express LYVE1. Meningeal angiogenesis is preceded by localization and proliferation of CD206⁺LYVE1⁺ wound-healing macrophages [162, 163]. Unique myeloid cell subsets were demonstrated to support meningeal vascular network repair in a mouse model of mTBI. Increased CD206⁺ macrophages around the lesion site stimulate angiogenesis by removing fibrin through MMP-2 production [161]. However, another study involving mTBI indicated that macrophages recruited to the injured dura mater have a minor impact on vascular regeneration. Compared with highly upregulated VEGF-A from macrophages in the pia mater, the expression of VEGF-A by macrophages in the dura mater did not significantly increase. These macrophages express low levels of pro-angiogenic molecules and high levels of pro-inflammatory molecules [5]. Further studies investigating the mechanism of meningeal vascular repair regulated by mLECs and other cell subtypes are warranted.

Glial cells Astrocytes are crucial for maintaining the integrity of the BBB. Mechanical tissue damage caused by TBI initiates a rapid increase in ATP released from astrocytes, followed by an increase in cytoplasmic calcium in reactive astrocytes surrounding the injured tissue. The calcium gradient recruits microglia to the lesion area, resulting in astrocyte and microglial reactivity [164–166]. After TBI, reactive astrocytes regulate the BBB [167] by producing and releasing VEGF, which increases the permeability of the BBB and leukocyte extravasation [168, 169]. By secreting apolipoprotein E and ramping up BBB permeability, astrocytes inhibit the

cyclophilin A–nuclear factor kappa-light-chain-enhancer of activated B cells–MMP-9 pathway in pericytes [170]. After CNS injury, Sonic hedgehog released by astrocytes exerts neuroprotective effects on multiple cell types [171, 172], and retinoic acid can also decrease BBB permeability [173]. In addition to impairing perivascular aquaporin (AQP)-4 polarization along endothelial surfaces after TBI, reactive astrocytes also alter the homeostasis of tissue fluid, resulting in edema [174, 175].

Microglia are parenchymal macrophages. Several studies have found that reactive microglia are crucial in boosting the angiogenic response to TBI. Angiogenic remodeling occurs within the penumbra in the first few days following ischemic insult [176, 177], and macrophages and microglia frequently surround angiogenic vasculature [178, 179]. M2 macrophages contribute to wound healing and vascular repair [140, 180, 181]. The mechanisms of M2 macrophage-mediated angiogenesis include the production of growth factors and pro-angiogenic cytokines (such as VEGF and FGF2) [140], releasing MMP-9 propeptide [181] and MMP-2 [161]. Reactive microglia enhance EC proliferation by changing the balance between tumor necrosis factor alpha (TNF- α) and transforming growth factor beta (TGF- β) [182]. A conditioned medium from M2 microglia treated with metformin stimulates angiogenesis *in vitro* by acting on ECs [183]. These findings suggest that microglia control angiogenesis and vascular repair following TBI [184].

Neurons Under both physiological [185] and pathological [186] settings, the neurological and circulatory systems are highly interdependent and share several regulatory molecules [187, 188]. In addition to the central role of neurons in functional recovery after TBI, they regulate vascular repair. Increased neurogenesis can be observed in the sub-ventricular zone around perilesional blood vessels after TBI [189, 190]. In a rat model of TBI, the administration of neural progenitor cells resulted in a transitory surge in angiogenesis adjacent to the lesion margin [191]. Trophic factors such as FGF2 and VEGF secreted by neural progenitors and stem cells promote angiogenesis [192].

Cytokines and chemokines regulate cellular responses in vascular repair after TBI Distinct cell types regulate differential events of cerebral vascular repair after TBI, including angiogenesis and vasculogenesis, the proliferation of ECs and smooth muscle cells, degradation of extracellular matrix and debris, stabilization of blood vessels, maintenance of BBB integrity, pruning of vasculature and neovascularization. These events are under the control of various cytokines and chemokines [9, 193, 194]. VEGFs, including at least five members (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E), are key regulators of angiogenesis and vasculogenesis in vascular repair after TBI through interacting with VEGF receptors (VEGFR1, VEGFR2, and VEGFR3) [76, 195, 196]. VEGFs regulate angiogenesis by promoting the proliferation,

migration and survival of ECs [197, 198] and incorporating EPCs into neovascularization foci [199]. However, VEGF-A, originally known as the vascular permeability factor, may be detrimental after TBI due to its role in facilitating edema and BBB permeability [200, 201]. FGF2 binds to FGF receptor-1 (FGFR-1) and FGFR-2 and regulates the processes of proliferation, migration survival of ECs and maintenance of the BBB [202–204]. MMPs are necessary for both pro- and anti-angiogenic processes through promoting ECs migration and tube formation, enhancing ECs growth, breaking intercellular adhesions, and cleavage of extracellular matrix [161, 205, 206]. IGF-1 promotes angiogenesis and neovascularization through stimulating migration and tube formation of ECs, regulating the inflammatory and vasodilatory response of ECs, and acting as a mitogen and antiapoptotic factor for vascular smooth muscle cells [207]. TGF- β regulates vascular repair through its effects on ECs and mural cells. TGF- β secreted by ECs can recruit mesenchymal cells to differentiate into smooth muscle cells and pericytes in perivascular space [208]. TGF- β exerts an angiogenic effect and promotes angiogenesis via binding to the complex of two cell-surface receptors, type II (T β RII) with activin receptor-like kinase-1 and endoglin [209]. TGF- β also exerts an anti-angiogenic effect via T β RII and activin receptor-like kinase-5 signaling to keep a quiescent state of ECs, which is required for the maturation of the vascular network [210]. TGF- β also influences vascular repair by regulating the proliferation and differentiation of smooth muscle cells and pericytes [211]. TNF- α is an inflammatory factor and interacts with TNF receptor 1/2. TNF- α regulates angiogenesis mediated by endothelial cells [212], macrophages [213] and endothelial progenitor cells [214]. Nitric oxide (NO) can exert both pro-angiogenic and anti-angiogenic functions by regulating the expression of FGF2, VEGF, endostatin and MMPs [215–218]. In CNS, NO is mainly synthesized by nitric oxide synthase (NOS), such as neuronal NOS (nNOS) [219], endothelial NOS (eNOS) [220] and inducible NOS (iNOS) [221]. Increased eNOS and eNOS phosphorylation have been reported to mediate EC migration and reendothelialization induced by high-density lipoprotein cholesterol [222]. In the brain stimulated by VEGF, iNOS has been reported to mediate an increase in MMP activity and angiogenesis [223]. Vascular cell adhesion molecule-1 (VCAM-1) is expressed by ECs on the luminal and lateral sides and mediates adhesion and rolling of leukocytes under inflammatory conditions [224, 225]. An increase in VCAM-1 was observed after stimulating ECs with VEGF [226, 227]. Soluble forms of VCAM-1 and E-selectin can exert an angiogenic effect by acting on ECs through a sialyl Lewis-X-dependent mechanism [228].

Therapeutic perspective

Numerous drugs have exhibited protective benefits in pre-clinical studies by reducing vascular damage and encouraging angiogenesis. Glibenclamide may reduce edema and subsequent hemorrhage in the CNS by acting on cerebral microvessels and stimulating neurogenesis by inhibiting

sulfonylurea receptor-1 [229]. Atorvastatin may preserve vascular repair after TBI by reducing secondary injury via anti-inflammatory and anti-oxidative mechanisms and increasing circulating EPCs levels [115]. Further, earlier studies showed that atorvastatin improved vascular remodeling via EPC mobilization in models of coronary heart disease and hindlimb ischemia [111, 230]. In models of ischemic stroke, sildenafil boosted CBF and promoted angiogenesis, neurogenesis and axonal remodeling surrounding the infarct site [231–233]. In a transgenic Alzheimer's disease mouse model and in *in vitro* studies, sunitinib was found to blunt the expression of thrombin, TNF- α , IL-1 β , MMP-9 and IL-6 by cerebrovasculature and improve cognitive behaviors in Alzheimer's disease mice by targeting VEGF and PDGF receptors [234]. Increased microvascular density, and decreased BBB leakage and brain water content can be observed after exogenous administration of mesenchymal stem cells and EPCs after TBI [235, 236]. Exogenous administration of angiogenic cytokines or chemokines was found to preserve BBB integrity [204] and promote the generation of tissue repair macrophages [237] and angiogenesis [238, 239]. These findings suggest that drugs that modulate key cells and molecules in vascular repair have the potential to improve clinical outcomes following TBI. A major focus of TBI studies is biomarkers that may help to define TBI severity (such as detecting concussion, detecting intracranial injury, which needs a head CT scan, and predicting delayed recovery and adverse outcome after TBI [240]) and guide a more precise strategy for the treatment of the heterogeneous condition of TBI. Fluid biomarkers of TBI are derived from cerebrospinal fluid, blood, saliva, urine and tears. Neuron-specific enolase, ubiquitin C-terminal hydrolase-L1, brain-derived neurotrophic factor, tau, amyloid- β , α II-spectrin breakdown products, myelin basic protein and S100-B can be used to reflect neuronal, axonal and astroglial injuries [241]. The CSF serum albumin ratio [242], protein components of tight junctions [243], VEGF and circulating extracellular vesicles are reported to be related to cerebral vascular injury and BBB leakage [241, 244]. Besides fluid biomarkers, vascular injury, microhemorrhages, CBF changes and BBB impairment can be indicated by neuroimaging biomarkers, such as functional MRI, arterial spin labeling, susceptibility weighted imaging, quantitative susceptibility mapping and contrast-enhanced imaging of MRI techniques [244]. For more information about biomarkers of TBI and vascular-directed therapeutic strategies, readers are encouraged to refer to recent reviews [8, 244, 245].

Conclusions

TBI is a life-threatening condition, and even mTBI may induce long-lasting symptoms related to defective vascular repair. Various cells contribute to vascular repair under the control of cytokines and chemokines released following TBI. Therapeutic approaches that target vascular repair by controlling key cells are promising in TBI treatment.

Abbreviations

BBB: Blood–brain barrier; CBF: Cerebral blood flow; CNS: Central nervous system; CSF: Cerebral spinal fluid; CT: Computerized tomography; EC: Endothelial cell; EM: Electron microscopy; FGF: fibroblast growth factor; IL-4: Interleukin 4; LYVE1: Lymphatic endothelial cell marker hyaluronan receptor 1; mLEC: Meningeal lymphatic endothelial cells; MMP: Matrix metalloproteinase; MRI: Magnetic resonance imaging; mTBI: Mild traumatic brain injury; PVM: Perivascular macrophage; TBI: Traumatic brain injury; TGF- β : Transforming growth factor beta; TJ: Tight junction; TNF- α : Tumor necrosis factor alpha; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular endothelial growth factor.

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Authors' contributions

ZAZ, LLY, JW and FY drafted and revised the manuscript. ZAZ, YL and LLY carried out the literature search and categorization of references. ZAZ contributed to the Figure drawing. HXS contributed to the design and critically edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Coronado VG, Xu L, Basavaraju SV, McGuire LC, Wald MM, Faul MD, et al. Surveillance for traumatic brain injury-related deaths—United States, 1997–2007. *MMWR Surveill Summ*. 2011;60:1–32.
2. Bazarian JJ, Pope C, McClung J, Cheng YT, Flesher W. Ethnic and racial disparities in emergency department care for mild traumatic brain injury. *Acad Emerg Med*. 2003;10:1209–17.
3. Stubbs JL, Thornton AE, Sevick JM, Silverberg ND, Barr AM, Honer WG, et al. Traumatic brain injury in homeless and marginally housed individuals: a systematic review and meta-analysis. *Lancet Public Health*. 2020;5:e19–32.
4. Farrer TJ, Hedges DW. Prevalence of traumatic brain injury in incarcerated groups compared to the general population: a meta-analysis. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2011;35:390–4.
5. Koh BI, Lee HJ, Kwak PA, Yang MJ, Kim JH, Kim HS, et al. VEGFR2 signaling drives meningeal vascular regeneration upon head injury. *Nat Commun*. 2020;11:3866.

6. Donovan V, Bianchi A, Hartman R, Bhanu B, Carson MJ, Obenaus A. Computational analysis reveals increased blood deposition following repeated mild traumatic brain injury. *Neuroimage Clin*. 2012;1:18–28.
7. Lynch CE, Crynen G, Ferguson S, Mouzon B, Paris D, Ojo J, et al. Chronic cerebrovascular abnormalities in a mouse model of repetitive mild traumatic brain injury. *Brain Inj*. 2016;30:1414–27.
8. Sandsmark DK, Bashir A, Wellington CL, Diaz-Arrastia R. Cerebral microvascular injury: a potentially treatable Endophenotype of traumatic brain injury-induced neurodegeneration. *Neuron*. 2019;103:367–79.
9. Salehi A, Zhang JH, Obenaus A. Response of the cerebral vasculature following traumatic brain injury. *J Cereb Blood Flow Metab*. 2017;37:2320–39.
10. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2:81–4.
11. Silverberg ND, Duhaime AC, Iaccarino MA. Mild traumatic brain injury in 2019–2020. *JAMA*. 2020;323:177–8.
12. Benson RR, Gattu R, Sewick B, Kou Z, Zakariah N, Cavanaugh JM, et al. Detection of hemorrhagic and axonal pathology in mild traumatic brain injury using advanced MRI: implications for neurorehabilitation. *NeuroRehabilitation*. 2012;31:261–79.
13. Konrad C, Geburek AJ, Rist F, Blumenroth H, Fischer B, Husstedt I, et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. *Psychol Med*. 2011;41:1197–211.
14. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol*. 2008;7:728–41.
15. Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med*. 2012;4:134ra60.
16. Dietrich WD, Alonso O, Halley M. Early microvascular and neuronal consequences of traumatic brain injury: a light and electron microscopic study in rats. *J Neurotrauma*. 1994;11:289–301.
17. Maxwell WL, Irvine A, Adams JH, Graham DI, Gennarelli TA. Response of cerebral microvasculature to brain injury. *J Pathol*. 1988;155:327–35.
18. Kenney K, Amyot F, Haber M, Pronger A, Bogoslovsky T, Moore C, et al. Cerebral vascular injury in traumatic brain injury. *Exp Neurol*. 2016;275:353–66.
19. Wang AC, Charters MA, Thawani JP, Than KD, Sullivan SE, Graziano GP. Evaluating the use and utility of noninvasive angiography in diagnosing traumatic blunt cerebrovascular injury. *J Trauma Acute Care Surg*. 2012;72:1601–10.
20. Mildenerberger W, Stifter SA, Greter M. Diversity and function of brain-associated macrophages. *Curr Opin Immunol*. 2022;76:102181.
21. Cugurra A, Mamuladze T, Rustenhoven J, Dykstra T, Beroshvili G, Greenberg ZJ, et al. Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. *Science*. 2021;373:eabf7844. <https://doi.org/10.1126/science.abf7844>.
22. Roth TL, Nayak D, Atanasijevic T, Koretsky AP, Latour LL, McGavern DB. Transcranial amelioration of inflammation and cell death after brain injury. *Nature*. 2014;505:223–8.
23. Corsellis JA, Brierley JB. Observations on the pathology of insidious dementia following head injury. *J Ment Sci*. 1959;105:714–20.

24. Williams WH, Potter S, Ryland H. Mild traumatic brain injury and Postconcussion syndrome: a neuropsychological perspective. *J Neurol Neurosurg Psychiatry*. 2010;81:1116–22.
25. Maegele M, Schochl H, Menovsky T, Marechal H, Marklund N, Buki A, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. *Lancet Neurol*. 2017;16:630–47.
26. Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. *BMC Emerg Med*. 2009;9:15.
27. Lee JJ, Segar DJ, Morrison JF, Mangham WM, Lee S, Asaad WF. Subdural hematoma as a major determinant of short-term outcomes in traumatic brain injury. *J Neurosurg*. 2018;128:236–49.
28. Hochstadter E, Stewart TC, Alharfi IM, Ranger A, Fraser DD. Subarachnoid hemorrhage prevalence and its association with short-term outcome in pediatric severe traumatic brain injury. *Neurocrit Care*. 2014;21:505–13.
29. Gaasch JA, Lockman PR, Geldenhuys WJ, Allen DD, Van der Schyf CJ. Brain iron toxicity: differential responses of astrocytes, neurons, and endothelial cells. *Neurochem Res*. 2007;32:1196–208.
30. Glushakova OY, Johnson D, Hayes RL. 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*. 2014;31:1180–93.
31. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. *Acta Neurochir*. 2008;150:165–75 discussion 75.
32. Midura EF, Jernigan PL, Kuethe JW, Friend LA, Veile R, Makley AT, et al. Microparticles impact coagulation after traumatic brain injury. *J Surg Res*. 2015;197:25–31.
33. Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT. Coagulopathy after traumatic brain injury. *Neurosurgery*. 2012;70:1334–45.
34. Schnuriger B, Inaba K, Abdelsayed GA, Lustenberger T, Eberle BM, Barmparas G, et al. The impact of platelets on the progression of traumatic intracranial hemorrhage. *J Trauma*. 2010;68:881–5.
35. Bhowmick S, D'Mello V, Caruso D, Wallerstein A, Abdul-Muneer PM. Impairment of pericyte-endothelium crosstalk leads to blood-brain barrier dysfunction following traumatic brain injury. *Exp Neurol*. 2019;317:260–70.
36. Cash A, Theus MH. Mechanisms of blood-brain barrier dysfunction in traumatic brain injury. *Int J Mol Sci*. 2020;21:3344. <https://doi.org/10.3390/ijms21093344>.
37. Rinder L, Olsson Y. Studies on vascular permeability changes in experimental brain concussion. I. Distribution of circulating fluorescent indicators in brain and cervical cord after sudden mechanical loading of the brain. *Acta Neuropathol*. 1968;11:183–200.
38. Hekmatpanah J, Hekmatpanah CR. Microvascular alterations following cerebral contusion in rats. Light, scanning, and electron microscope study. *J Neurosurg*. 1985;62:888–97.
39. Donkin JJ, Vink R. Mechanisms of cerebral edema in traumatic brain injury: therapeutic developments. *Curr Opin Neurol*. 2010;23:293–9.
40. Yeoh S, Bell ED, Monson KL. Distribution of blood-brain barrier disruption in primary blast injury. *Ann Biomed Eng*. 2013;41:2206–14.
41. Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. *Pharmacol Rev*. 2005;57:173–85.
42. Keaney J, Campbell M. The dynamic blood-brain barrier. *FEBS J*. 2015;282:4067–79.
43. Ho KM, Honeybul S, Yip CB, Silbert BI. Prognostic significance of blood-brain barrier disruption in patients with severe nonpenetrating traumatic brain injury requiring decompressive craniectomy. *J Neurosurg*. 2014;121:674–9.
44. Tomkins O, Shelef I, Kaizerman I, Eliushin A, Afawi Z, Misk A, et al. Blood-brain barrier disruption in post-traumatic epilepsy. *J Neurol Neurosurg Psychiatry*. 2008;79:774–7.
45. Habgood MD, Bye N, Dziegielewska KM, Ek CJ, Lane MA, Potter A, et al. Changes in blood-brain barrier permeability to large and small molecules following traumatic brain injury in mice. *Eur J Neurosci*. 2007;25:231–8.
46. Marmarou A. Pathophysiology of traumatic brain edema: current concepts. *Acta Neurochir Suppl*. 2003;86:7–10.
47. Badaut J, Ashwal S, Obenaus A. Aquaporins in cerebrovascular disease: a target for treatment of brain edema? *Cerebrovasc Dis*. 2011;31:521–31.
48. Nirula R, Millar D, Greene T, McFadden M, Shah L, Scalea TM, et al. Decompressive craniectomy or medical management for refractory intracranial hypertension: an AAST-MIT propensity score analysis. *J Trauma Acute Care Surg*. 2014;76:944–52 discussion 52–5.
49. Barzo P, Marmarou A, Fatouros P, Hayasaki K, Corwin F. Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging. *J Neurosurg*. 1997;87:900–7.
50. Hanstock CC, Faden AI, Bendall MR, Vink R. Diffusion-weighted imaging differentiates ischemic tissue from traumatized tissue. *Stroke*. 1994;25:843–8.
51. Mestre H, Du T, Sweeney AM, Liu G, Samson AJ, Peng W, et al. Cerebrospinal fluid influx drives acute ischemic tissue swelling. *Science*. 2020;367:eaax7171.
52. Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. *J Neurosurg*. 1992;77:360–8.
53. Soustiel JF, Glenn TC, Shik V, Boscardin J, Mahamid E, Zaaroor M. Monitoring of cerebral blood flow and metabolism in traumatic brain injury. *J Neurotrauma*. 2005;22:955–65.
54. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT investigators. Prolyse in acute cerebral thromboembolism. *Stroke*. 1998;29:4–11.
55. Ostergaard L, Engedal TS, Aamand R, Mikkelsen R, Iversen NK, Anzabi M, et al. Capillary transit time heterogeneity and flow-metabolism coupling after traumatic brain injury. *J Cereb Blood Flow Metab*. 2014;34:1585–98.
56. Doshi H, Wiseman N, Liu J, Wang W, Welch RD, O'Neil BJ, et al. Cerebral hemodynamic changes of mild traumatic brain injury at the acute stage. *PLoS One*. 2015;10:e0118061.
57. Albrecht JS, Liu X, Smith GS, Baumgarten M, Rattinger GB, Gambert SR, et al. Stroke incidence following traumatic brain injury in older adults. *J Head Trauma Rehabil*. 2015;30:E62–7.
58. Chen YH, Kang JH, Lin HC. Patients with traumatic brain injury: population-based study suggests increased risk of stroke. *Stroke*. 2011;42:2733–9.

59. Liao CC, Chou YC, Yeh CC, Hu CJ, Chiu WT, Chen TL. Stroke risk and outcomes in patients with traumatic brain injury: 2 nationwide studies. *Mayo Clin Proc.* 2014;89:163–72.
60. Laune Y, Fryer TD, Hong YT, Steiner LA, Nortje J, Veenith TV, et al. Spatial and temporal pattern of ischemia and abnormal vascular function following traumatic brain injury. *JAMA Neurol.* 2020;77:339–49.
61. Veenith TV, Carter EL, Geeraerts T, Grossac J, Newcombe VF, Outtrim J, et al. Pathophysiologic mechanisms of cerebral ischemia and diffusion hypoxia in traumatic brain injury. *JAMA Neurol.* 2016;73:542–50.
62. Vespa PM. Brain hypoxia and ischemia after traumatic brain injury: is oxygen the right metabolic target? *JAMA Neurol.* 2016;73:504–5.
63. Budohoski KP, Czosnyka M, de Riva N, Smielewski P, Pickard JD, Menon DK, et al. The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. *Neurosurgery.* 2012;71:652–60 discussion 60-1.
64. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke.* 1996;27:1829–34.
65. Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD. Cerebral autoregulation following head injury. *J Neurosurg.* 2001;95:756–63.
66. Johnson U, Nilsson P, Ronne-Engstrom E, Howells T, Enblad P. Favorable outcome in traumatic brain injury patients with impaired cerebral pressure autoregulation when treated at low cerebral perfusion pressure levels. *Neurosurgery.* 2011;68:714–21 discussion 21-2.
67. Kramer DR, Winer JL, Pease BA, Amar AP, Mack WJ. Cerebral vasospasm in traumatic brain injury. *Neurol Res Int.* 2013;2013:1–7.
68. Oertel M, Boscardin WJ, Obrist WD, Glenn TC, McArthur DL, Gravori T, et al. Posttraumatic vasospasm: the epidemiology, severity, and time course of an underestimated phenomenon: a prospective study performed in 299 patients. *J Neurosurg.* 2005;103:812–24.
69. Alford PW, Dabiri BE, Goss JA, Hemphill MA, Brigham MD, Parker KK. Blast-induced phenotypic switching in cerebral vasospasm. *Proc Natl Acad Sci U S A.* 2011;108:12705–10.
70. Izzy S, Muehlschlegel S. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage and traumatic brain injury. *Curr Treat Options Neurol.* 2014;16:278.
71. Dore-Duffy P, Owen C, Balabanov R, Murphy S, Beaumont T, Rafols JA. Pericyte migration from the vascular wall in response to traumatic brain injury. *Microvasc Res.* 2000;60:55–69.
72. Park E, Bell JD, Siddiq IP, Baker AJ. An analysis of regional microvascular loss and recovery following two grades of fluid percussion trauma: a role for hypoxia-inducible factors in traumatic brain injury. *J Cereb Blood Flow Metab.* 2009;29:575–84.
73. Siddiq I, Park E, Liu E, Spratt SK, Surosky R, Lee G, et al. Treatment of traumatic brain injury using zinc-finger protein gene therapy targeting VEGF-A. *J Neurotrauma.* 2012;29:2647–59.
74. Quintard H, Heurteaux C, Ichaï C. Adult neurogenesis and brain remodelling after brain injury: from bench to bedside? *Anaesth Crit Care Pain Med.* 2015;34:239–45.
75. Greenberg DA, Jin K. From angiogenesis to neuropathology. *Nature.* 2005;438:954–9.
76. Risau W. Mechanisms of angiogenesis. *Nature.* 1997;386:671–4.
77. Skold MK, von Gertten C, Sandberg-Nordqvist AC, Mathiesen T, Holmin S. VEGF and VEGF receptor expression after experimental brain contusion in rat. *J Neurotrauma.* 2005;22:353–67.
78. Shore PM, Jackson EK, Wisniewski SR, Clark RS, Adelson PD, Kochanek PM. Vascular endothelial growth factor is increased in cerebrospinal fluid after traumatic brain injury in infants and children. *Neurosurgery.* 2004;54:605–11 discussion 11-2.
79. Ju S, Xu C, Wang G, Zhang L. VEGF-C induces alternative activation of microglia to promote recovery from traumatic brain injury. *J Alzheimers Dis.* 2019;68:1687–97.
80. Ma X, Agas A, Siddiqui Z, Kim K, Iglesias-Montoro P, Kalluru J, et al. Angiogenic peptide hydrogels for treatment of traumatic brain injury. *Bioact Mater.* 2020;5:124–32.
81. Zhang Y, Xu B, Chen Q, Yan Y, Du J, Du X. Apoptosis of endothelial cells contributes to brain vessel pruning of zebrafish during development. *Front Mol Neurosci.* 2018;11:222.
82. Alves JL. Blood-brain barrier and traumatic brain injury. *J Neurosci Res.* 2014;92:141–7.
83. Chodobski A, Zink BJ, Szmydynger-Chodobska J. Blood-brain barrier pathophysiology in traumatic brain injury. *Transl Stroke Res.* 2011;2:492–516.
84. Charkviani M, Muradashvili N, Lominadze D. Vascular and non-vascular contributors to memory reduction during traumatic brain injury. *Eur J Neurosci.* 2019;50:2860–76.
85. Eliceiri BP, Paul R, Schwartzberg PL, Hood JD, Leng J, Cheresch DA. Selective requirement for Src kinases during VEGF-induced angiogenesis and vascular permeability. *Mol Cell.* 1999;4:915–24.
86. Heymans S, Luttun A, Nuyens D, Theilmeier G, Creemers E, Moons L, et al. Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure. *Nat Med.* 1999;5:1135–42.
87. Eelen G, de Zeeuw P, Simons M, Carmeliet P. Endothelial cell metabolism in normal and diseased vasculature. *Circ Res.* 2015;116:1231–44.
88. Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. *Cell.* 2011;146:873–87.
89. Mazzone M, Dettori D, de Oliveira RL, Loges S, Schmidt T, Jonckx B, et al. Heterozygous deficiency of PHD2 restores tumor oxygenation and inhibits metastasis via endothelial normalization. *Cell.* 2009;136:839–51.
90. Komarova YA, Kruse K, Mehta D, Malik AB. Protein interactions at endothelial junctions and Signaling mechanisms regulating endothelial permeability. *Circ Res.* 2017;120:179–206.
91. Schneeberger EE, Lynch RD. The tight junction: a multifunctional complex. *Am J Physiol Cell Physiol.* 2004;286:C1213–28.
92. Hu X, De Silva TM, Chen J, Faraci FM. Cerebral vascular disease and neurovascular injury in ischemic stroke. *Circ Res.* 2017;120:449–71.
93. Kempuraj D, Ahmed ME, Selvakumar GP, Thangavel R, Raikwar SP, Zaheer SA, et al. Mast cell activation, Neuroinflammation, and tight junction protein derangement in acute traumatic brain injury. *Mediat Inflamm.* 2020;2020:4243953.

94. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med*. 2000;6:389–95.
95. Boroujerdi A, Welser-Alves JV, Milner R. Matrix metalloproteinase-9 mediates post-hypoxic vascular pruning of cerebral blood vessels by degrading laminin and claudin-5. *Angiogenesis*. 2015;18:255–64.
96. Adams RH, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. *Nat Rev Mol Cell Biol*. 2007;8:464–78.
97. Herbert SP, Stainier DY. Molecular control of endothelial cell behaviour during blood vessel morphogenesis. *Nat Rev Mol Cell Biol*. 2011;12:551–64.
98. Korn C, Augustin HG. Mechanisms of vessel pruning and regression. *Dev Cell*. 2015;34:5–17.
99. Betz C, Lenard A, Belting HG, Affolter M. Cell behaviors and dynamics during angiogenesis. *Development*. 2016;143:2249–60.
100. Kochhan E, Lenard A, Ellertsdottir E, Herwig L, Affolter M, Belting HG, et al. Blood flow changes coincide with cellular rearrangements during blood vessel pruning in zebrafish embryos. *PLoS One*. 2013;8:e75060.
101. Franco CA, Jones ML, Bernabeu MO, Geudens I, Mathivet T, Rosa A, et al. Dynamic endothelial cell rearrangements drive developmental vessel regression. *PLoS Biol*. 2015;13:e1002125.
102. Lobov IB, Rao S, Carroll TJ, Vallance JE, Ito M, Ondr JK, et al. WNT7b mediates macrophage-induced programmed cell death in patterning of the vasculature. *Nature*. 2005;437:417–21.
103. Liu L, Wei H, Chen F, Wang J, Dong JF, Zhang J. Endothelial progenitor cells correlate with clinical outcome of traumatic brain injury. *Crit Care Med*. 2011;39:1760–5.
104. Wei HJ, Liu L, Chen FL, Wang D, Wang L, Wang ZG, et al. Decreased numbers of circulating endothelial progenitor cells are associated with hyperglycemia in patients with traumatic brain injury. *Neural Regen Res*. 2019;14:984–90.
105. Liu L, Liu H, Jiao J, Liu H, Bergeron A, Dong JF, et al. Changes in circulating human endothelial progenitor cells after brain injury. *J Neurotrauma*. 2007;24:936–43.
106. Guo X, Liu L, Zhang M, Bergeron A, Cui Z, Dong JF, et al. Correlation of CD34+ cells with tissue angiogenesis after traumatic brain injury in a rat model. *J Neurotrauma*. 2009;26:1337–44.
107. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science*. 1997;275:964–7.
108. Kawamoto A, Gwon HC, Iwaguro H, Yamaguchi JI, Uchida S, Masuda H, et al. Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia. *Circulation*. 2001;103:634–7.
109. Britten MB, Abolmaali ND, Assmus B, Lehmann R, Honold J, Schmitt J, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. *Circulation*. 2003;108:2212–8.
110. Schachinger V, Assmus B, Britten MB, Honold J, Lehmann R, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI trial. *J Am Coll Cardiol*. 2004;44:1690–9.
111. Matsumura M, Fukuda N, Kobayashi N, Umezawa H, Takasaka A, Matsumoto T, et al. Effects of atorvastatin on angiogenesis in hindlimb ischemia and endothelial progenitor cell formation in rats. *J Atheroscler Thromb*. 2009;16:319–26.
112. Kalka C, Masuda H, Takahashi T, Kalka-Moll WM, Silver M, Kearney M, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. *Proc Natl Acad Sci U S A*. 2000;97:3422–7.
113. Takahashi T, Kalka C, Masuda H, Chen D, Silver M, Kearney M, et al. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. *Nat Med*. 1999;5:434–8.
114. Li Z, Wang B, Kan Z, Zhang B, Yang Z, Chen J, et al. Progesterone increases circulating endothelial progenitor cells and induces neural regeneration after traumatic brain injury in aged rats. *J Neurotrauma*. 2012;29:343–53.
115. Wang B, Sun L, Tian Y, Li Z, Wei H, Wang D, et al. Effects of atorvastatin in the regulation of circulating EPCs and angiogenesis in traumatic brain injury in rats. *J Neurol Sci*. 2012;319:117–23.
116. Yip HK, Tsai TH, Lin HS, Chen SF, Sun CK, Leu S, et al. Effect of erythropoietin on level of circulating endothelial progenitor cells and outcome in patients after acute ischemic stroke. *Crit Care*. 2011;15:R40.
117. Ran QS, Yu YH, Fu XH, Wen YC. Activation of the notch signaling pathway promotes neurovascular repair after traumatic brain injury. *Neural Regen Res*. 2015;10:1258–64.
118. Ma F, Moranco A, Montaner J, Rosell A. Endothelial progenitor cells and revascularization following stroke. *Brain Res*. 2015;1623:150–9.
119. Senger DR, Perruzzi CA, Feder J, Dvorak HF. A highly conserved vascular permeability factor secreted by a variety of human and rodent tumor cell lines. *Cancer Res*. 1986;46:5629–32.
120. Connolly DT, Heuvelman DM, Nelson R, Olander JV, Eppley BL, Delfino JJ, et al. Tumor vascular permeability factor stimulates endothelial cell growth and angiogenesis. *J Clin Invest*. 1989;84:1470–8.
121. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science*. 1989;246:1306–9.
122. Asahara T, Takahashi T, Masuda H, Kalka C, Chen D, Iwaguro H, et al. VEGF contributes to postnatal neovascularization by mobilizing bone marrow-derived endothelial progenitor cells. *EMBO J*. 1999;18:3964–72.
123. Hattori K, Dias S, Heissig B, Hackett NR, Lyden D, Tateno M, et al. Vascular endothelial growth factor and angiopoietin-1 stimulate postnatal hematopoiesis by recruitment of vasculogenic and hematopoietic stem cells. *J Exp Med*. 2001;193:1005–14.
124. Fernandez-Klett F, Offenhauser N, Dirnagl U, Priller J, Lindauer U. Pericytes in capillaries are contractile in vivo, but arterioles mediate functional hyperemia in the mouse brain. *Proc Natl Acad Sci U S A*. 2010;107:22290–5.
125. Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*. 2014;508:55–60.
126. Armulik A, Genove G, Mae M, Nisancioglu MH, Wallgard E, Niaudet C, et al. Pericytes regulate the blood-brain barrier. *Nature*. 2010;468:557–61.

127. Daneman R, Zhou L, Kebede AA, Barres BA. Pericytes are required for blood-brain barrier integrity during embryogenesis. *Nature*. 2010;468:562–6.
128. Chan-Ling T, Page MP, Gardiner T, Baxter L, Rosinova E, Hughes S. Desmin ensheathment ratio as an indicator of vessel stability: evidence in normal development and in retinopathy of prematurity. *Am J Pathol*. 2004;165:1301–13.
129. Cheng J, Korte N, Nortley R, Sethi H, Tang Y, Attwell D. Targeting pericytes for therapeutic approaches to neurological disorders. *Acta Neuropathol*. 2018;136:507–23.
130. Raza A, Franklin MJ, Dudek AZ. Pericytes and vessel maturation during tumor angiogenesis and metastasis. *Am J Hematol*. 2010;85:593–8.
131. Bergers G, Song S. The role of pericytes in blood-vessel formation and maintenance. *Neuro-Oncology*. 2005;7:452–64.
132. Zehendner CM, Sebastiani A, Hugonnet A, Bischoff F, Luhmann HJ, Thal SC. Traumatic brain injury results in rapid pericyte loss followed by reactive pericytosis in the cerebral cortex. *Sci Rep*. 2015;5:13497.
133. Dore-Duffy P, Wang X, Mehedi A, Kreipke CW, Rafols JA. Differential expression of capillary VEGF isoforms following traumatic brain injury. *Neurol Res*. 2007;29:395–403.
134. Yemisci M, Gursay-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med*. 2009;15:1031–7.
135. Hong H, Tian XY. The role of macrophages in vascular repair and regeneration after ischemic injury. *Int J Mol Sci*. 2020;21:6328. <https://doi.org/10.3390/ijms21176328>.
136. la Sala A, Pontecorvo L, Agresta A, Rosano G, Stabile E. Regulation of collateral blood vessel development by the innate and adaptive immune system. *Trends Mol Med*. 2012;18:494–501.
137. Nakayama T, Kurobe H, Sugawara N, Kinoshita H, Higashida M, Matsuoka Y, et al. Role of macrophage-derived hypoxia-inducible factor (HIF)-1 α as a mediator of vascular remodelling. *Cardiovasc Res*. 2013;99:705–15.
138. Hsieh CL, Kim CC, Ryba BE, Niemi EC, Bando JK, Locksley RM, et al. Traumatic brain injury induces macrophage subsets in the brain. *Eur J Immunol*. 2013;43:2010–22.
139. Huber-Lang M, Lambris JD, Ward PA. Innate immune responses to trauma. *Nat Immunol*. 2018;19:327–41.
140. Jetten N, Verbruggen S, Gijbels MJ, Post MJ, De Winther MP, Donners MM. Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. *Angiogenesis*. 2014;17:109–18.
141. Spiller KL, Anfang RR, Spiller KJ, Ng J, Nakazawa KR, Daulton JW, et al. The role of macrophage phenotype in vascularization of tissue engineering scaffolds. *Biomaterials*. 2014;35:4477–88.
142. He H, Mack JJ, Guc E, Warren CM, Squadrito ML, Kilarski WW, et al. Perivascular macrophages limit permeability. *Arterioscler Thromb Vasc Biol*. 2016;36:2203–12.
143. Zhang Z, Zhang ZY, Wu Y, Schluesener HJ. Lesional accumulation of CD163+ macrophages/microglia in rat traumatic brain injury. *Brain Res*. 2012;1461:102–10.
144. Mastorakos P, Russo MV, Zhou T, Johnson K, McGavern DB. Antimicrobial immunity impedes CNS vascular repair following brain injury. *Nat Immunol*. 2021;22:1280–93.
145. Da Mesquita S, Fu Z, Kipnis J. The meningeal lymphatic system: a new player in neurophysiology. *Neuron*. 2018;100:375–88.
146. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. 2015;212:991–9.
147. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015;523:337–41.
148. Ahn JH, Cho H, Kim JH, Kim SH, Ham JS, Park I, et al. Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. *Nature*. 2019;572:62–6.
149. Rustenhoven J, Drieu A, Mamuladze T, de Lima KA, Dykstra T, Wall M, et al. Functional characterization of the dural sinuses as a neuroimmune interface. *Cell*. 2021;184:1000–16 e27.
150. Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature*. 2018;560:185–91.
151. Liao J, Zhang M, Shi Z, Lu H, Wang L, Fan W, et al. Improving the function of meningeal lymphatic vessels to promote brain edema absorption after TBI. *J Neurotrauma*. 2023;40:383–94.
152. Loane DJ, Faden AI. Traumatic meningeal injury and repair mechanisms. *Nat Immunol*. 2018;19:431–2.
153. Bolte AC, Dutta AB, Hurt ME, Smirnov I, Kovacs MA, McKee CA, et al. Meningeal lymphatic dysfunction exacerbates traumatic brain injury pathogenesis. *Nat Commun*. 2020;11:4524.
154. Meng FW, Yu JT, Chen JY, Yang PF. New lymphatic cell formation is associated with damaged brain tissue clearance after penetrating traumatic brain injury. *Sci Rep*. 2021;11:10193.
155. Chen J, He J, Ni R, Yang Q, Zhang Y, Luo L. Cerebrovascular injuries induce lymphatic invasion into brain parenchyma to guide vascular regeneration in zebrafish. *Dev Cell*. 2019;49:697–710.e5.
156. Mauri C, van Impel A, Mackay EW, Schulte-Merker S. The adaptor protein Grb2b is an essential modulator for lymphovenous sprout formation in the zebrafish trunk. *Angiogenesis*. 2021;24:345–62.
157. Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature*. 2010;468:253–62.
158. Prinz M, Priller J, Sisodia SS, Ransohoff RM. Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. *Nat Neurosci*. 2011;14:1227–35.
159. Prinz M, Priller J. Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. *Nat Rev Neurosci*. 2014;15:300–12.
160. Goldmann T, Wieghofer P, Jordao MJ, Prutek F, Hagemeyer N, Frenzel K, et al. Origin, fate and dynamics of macrophages at central nervous system interfaces. *Nat Immunol*. 2016;17:797–805.
161. Russo MV, Latour LL, McGavern DB. Distinct myeloid cell subsets promote meningeal remodeling and vascular repair after mild traumatic brain injury. *Nat Immunol*. 2018;19:442–52.
162. Schledzewski K, Falkowski M, Moldenhauer G, Metharom P, Kzyshkowska J, Ganss R, et al. Lymphatic endothelium-specific hyaluronan receptor LYVE-1 is expressed by stabilin-1+, F4/80+, CD11b+ macrophages in malignant tumours and wound healing tissue in vivo and in bone marrow cultures in

- vitro: implications for the assessment of lymphangiogenesis. *J Pathol.* 2006;209:67–77.
163. Cho CH, Koh YJ, Han J, Sung HK, Jong Lee H, Morisada T, et al. Angiogenic role of LYVE-1-positive macrophages in adipose tissue. *Circ Res.* 2007;100:e47–57.
 164. Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, et al. ATP mediates rapid microglial response to local brain injury in vivo. *Nat Neurosci.* 2005;8:752–8.
 165. Kim JV, Dustin ML. Innate response to focal necrotic injury inside the blood-brain barrier. *J Immunol.* 2006;177: 5269–77.
 166. Zhao Z-A, Li P, Ye S-Y, Ning Y-L, Wang H, Peng Y, et al. Perivascular AQP4 dysregulation in the hippocampal CA1 area after traumatic brain injury is alleviated by adenosine A2A receptor inactivation. *Sci Rep.* 2017;7:2254.
 167. Bush TG, Puvanachandra N, Horner CH, Polito A, Ostensfeld T, Svendsen CN, et al. Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. *Neuron.* 1999;23:297–308.
 168. Argaw AT, Gurfein BT, Zhang Y, Zameer A, John GR. VEGF-mediated disruption of endothelial CLN-5 promotes blood-brain barrier breakdown. *Proc Natl Acad Sci U S A.* 2009;106:1977–82.
 169. Argaw AT, Asp L, Zhang J, Navrazhina K, Pham T, Mariani JN, et al. Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. *J Clin Invest.* 2012;122:2454–68.
 170. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin a. *Nature.* 2012;485:512–6.
 171. Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, et al. The hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. *Science.* 2011;334:1727–31.
 172. Alvarez JI, Katayama T, Prat A. Glial influence on the blood brain barrier. *Glia.* 2013;61:1939–58.
 173. Mizee MR, Nijland PG, van der Pol SM, Drexhage JA, van Het Hof B, Mebius R, et al. Astrocyte-derived retinoic acid: a novel regulator of blood-brain barrier function in multiple sclerosis. *Acta Neuropathol.* 2014;128:691–703.
 174. Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. *Nat Rev Neurosci.* 2013;14:265–77.
 175. Burda JE, Bernstein AM, Sofroniew MV. Astrocyte roles in traumatic brain injury. *Exp Neurol.* 2016;275:305–15.
 176. Chen HH, Chien CH, Liu HM. Correlation between angiogenesis and basic fibroblast growth factor expression in experimental brain infarct. *Stroke.* 1994;25:1651–7.
 177. Wei L, Erinjeri JP, Rovainen CM, Woolsey TA. Collateral growth and angiogenesis around cortical stroke. *Stroke.* 2001;32:2179–84.
 178. Jander S, Schroeter M, D'Urso D, Gillen C, Witte OW, Stoll G. Focal ischaemia of the rat brain elicits an unusual inflammatory response: early appearance of CD8+ macrophages/microglia. *Eur J Neurosci.* 1998;10:680–8.
 179. Manoonkitiwongsa PS, Jackson-Friedman C, McMillan PJ, Schultz RL, Lyden PD. Angiogenesis after stroke is correlated with increased numbers of macrophages: the clean-up hypothesis. *J Cereb Blood Flow Metab.* 2001;21:1223–31.
 180. Medina RJ, O'Neill CL, O'Doherty TM, Knott H, Guduric-Fuchs J, Gardiner TA, et al. Myeloid angiogenic cells act as alternative M2 macrophages and modulate angiogenesis through interleukin-8. *Mol Med.* 2011;17:1045–55.
 181. Zajac E, Schweighofer B, Kupriyanova TA, Juncker-Jensen A, Minder P, Quigley JP, et al. Angiogenic capacity of M1- and M2-polarized macrophages is determined by the levels of TIMP-1 complexed with their secreted proMMP-9. *Blood.* 2013;122:4054–67.
 182. Welser JV, Li L, Milner R. Microglial activation state exerts a biphasic influence on brain endothelial cell proliferation by regulating the balance of TNF and TGF-beta1. *J Neuroinflammation.* 2010;7:89.
 183. Jin Q, Cheng J, Liu Y, Wu J, Wang X, Wei S, et al. Improvement of functional recovery by chronic metformin treatment is associated with enhanced alternative activation of microglia/macrophages and increased angiogenesis and neurogenesis following experimental stroke. *Brain Behav Immun.* 2014;40:131–42.
 184. Loane DJ, Kumar A. Microglia in the TBI brain: the good, the bad, and the dysregulated. *Exp Neurol.* 2016;275:316–27.
 185. Mukouyama YS, Shin D, Britsch S, Taniguchi M, Anderson DJ. Sensory nerves determine the pattern of arterial differentiation and blood vessel branching in the skin. *Cell.* 2002;109:693–705.
 186. Lambrechts D, Storkebaum E, Morimoto M, Del-Favero J, Desmet F, Marklund SL, et al. VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death. *Nat Genet.* 2003;34:383–94.
 187. Lu X, Le Noble F, Yuan L, Jiang Q, De Lafarge B, Sugiyama D, et al. The netrin receptor UNC5B mediates guidance events controlling morphogenesis of the vascular system. *Nature.* 2004;432:179–86.
 188. Okabe K, Kobayashi S, Yamada T, Kurihara T, Tai-Nagara I, Miyamoto T, et al. Neurons limit angiogenesis by titrating VEGF in retina. *Cell.* 2014;159:584–96.
 189. Parent JM, Vexler ZS, Gong C, Derugin N, Ferriero DM. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann Neurol.* 2002;52:802–13.
 190. Kojima T, Hirota Y, Ema M, Takahashi S, Miyoshi I, Okano H, et al. Subventricular zone-derived neural progenitor cells migrate along a blood vessel scaffold toward the post-stroke striatum. *Stem Cells.* 2010;28:545–54.
 191. Skardelly M, Gaber K, Burdack S, Scheidt F, Hilbig H, Boltze J, et al. Long-term benefit of human fetal neuronal progenitor cell transplantation in a clinically adapted model after traumatic brain injury. *J Neurotrauma.* 2011;28:401–14.
 192. Schiera G, Proia P, Alberti C, Mineo M, Savettieri G, Di Liegro I. Neurons produce FGF2 and VEGF and secrete them at least in part by shedding extracellular vesicles. *J Cell Mol Med.* 2007;11:1384–94.
 193. Addington CP, Roussas A, Dutta D, Stabenfeldt SE. Endogenous repair signaling after brain injury and complementary bioengineering approaches to enhance neural regeneration. *Biomark Insights.* 2015;10:43–60.
 194. Benelli R, Lorusso G, Albini A, Noonan DM. Cytokines and chemokines as regulators of angiogenesis in health and disease. *Curr Pharm Des.* 2006;12:3101–15.
 195. Hanahan D. Signaling vascular morphogenesis and maintenance. *Science.* 1997;277:48–50.
 196. Hamada K, Oike Y, Takakura N, Ito Y, Jussila L, Dumont DJ, et al. VEGF-C signaling pathways through VEGFR-2 and

- VEGFR-3 in vasculoangiogenesis and hematopoiesis. *Blood*. 2000;96:3793–800.
197. Koch S, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. *Cold Spring Harb Perspect Med*. 2012;2:a006502.
 198. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev*. 2004;25:581–611.
 199. Asahara T, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res*. 1999;85:221–8.
 200. Sun M, Baker TL, Wilson CT, Brady RD, Mychasiuk R, Yamakawa GR, et al. Treatment with vascular endothelial growth factor-a worsens cognitive recovery in a rat model of mild traumatic brain injury. *Front Mol Neurosci*. 2022;15:937350.
 201. Croll SD, Ransohoff RM, Cai N, Zhang Q, Martin FJ, Wei T, et al. VEGF-mediated inflammation precedes angiogenesis in adult brain. *Exp Neurol*. 2004;187:388–402.
 202. Goetz R, Mohammadi M. Exploring mechanisms of FGF signalling through the lens of structural biology. *Nat Rev Mol Cell Biol*. 2013;14:166–80.
 203. Wang ZG, Cheng Y, Yu XC, Ye LB, Xia QH, Johnson NR, et al. bFGF protects against blood-brain barrier damage through junction protein regulation via PI3K-Akt-Rac1 pathway following traumatic brain injury. *Mol Neurobiol*. 2016;53:7298–311.
 204. Huang B, Krafft PR, Ma Q, Rolland WB, Caner B, Lekic T, et al. Fibroblast growth factors preserve blood-brain barrier integrity through RhoA inhibition after intracerebral hemorrhage in mice. *Neurobiol Dis*. 2012;46:204–14.
 205. Rundhaug JE. Matrix metalloproteinases and angiogenesis. *J Cell Mol Med*. 2005;9:267–85.
 206. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuna JM, Perez-Romero BA, Guerrero-Rodriguez JF, et al. The roles of matrix Metalloproteinases and their inhibitors in human diseases. *Int J Mol Sci*. 2020;21:9739.
 207. Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. *Arterioscler Thromb Vasc Biol*. 2004;24:435–44.
 208. Armulik A, Genove G, Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. *Dev Cell*. 2011;21:193–215.
 209. Goumans MJ, Valdimarsdottir G, Itoh S, Lebrin F, Larsson J, Mummery C, et al. Activin receptor-like kinase (ALK)1 is an antagonistic mediator of lateral TGFbeta/ALK5 signaling. *Mol Cell*. 2003;12:817–28.
 210. Goumans MJ, Lebrin F, Valdimarsdottir G. Controlling the angiogenic switch: a balance between two distinct TGF- β receptor signaling pathways. *Trends Cardiovasc Med*. 2003;13:301–7.
 211. Goumans MJ, Ten Dijke P. TGF- β Signaling in control of cardiovascular function. *Cold Spring Harb Perspect Biol*. 2018;10:a022210. <https://doi.org/10.1101/cshperspect.a022210>.
 212. Wang L, Chopp M, Teng H, Bolz M, Francisco MA, Aluigi DM, et al. Tumor necrosis factor alpha primes cerebral endothelial cells for erythropoietin-induced angiogenesis. *J Cereb Blood Flow Metab*. 2011;31:640–7.
 213. Leibovich SJ, Polverini PJ, Shepard HM, Wiseman DM, Shively V, Nuseir N. Macrophage-induced angiogenesis is mediated by tumour necrosis factor-alpha. *Nature*. 1987;329:630–2.
 214. Prisco AR, Hoffmann BR, Kaczorowski CC, McDermott-Roe C, Stodola TJ, Exner EC, et al. Tumor necrosis factor alpha regulates endothelial progenitor cell migration via CADM1 and NF-kB. *Stem Cells*. 2016;34:1922–33.
 215. Yamamoto N, Oyaizu T, Enomoto M, Horie M, Yuasa M, Okawa A, et al. VEGF and bFGF induction by nitric oxide is associated with hyperbaric oxygen-induced angiogenesis and muscle regeneration. *Sci Rep*. 2020;10:2744.
 216. Deininger MH, Wybranietz WA, Graepler FT, Lauer UM, Meyermann R, Schluesener HJ. Endothelial endostatin release is induced by general cell stress and modulated by the nitric oxide/cGMP pathway. *FASEB J*. 2003;17:1267–76.
 217. Sunshine SB, Dallabrida SM, Durand E, Ismail NS, Bazinet L, Birsner AE, et al. Endostatin lowers blood pressure via nitric oxide and prevents hypertension associated with VEGF inhibition. *Proc Natl Acad Sci U S A*. 2012;109:11306–11.
 218. Simao F, Pagnussat AS, Seo JH, Navaratna D, Leung W, Lok J, et al. Pro-angiogenic effects of resveratrol in brain endothelial cells: nitric oxide-mediated regulation of vascular endothelial growth factor and metalloproteinases. *J Cereb Blood Flow Metab*. 2012;32:884–95.
 219. Mayer B, John M, Bohme E. Purification of a Ca²⁺/calmodulin-dependent nitric oxide synthase from porcine cerebellum. Cofactor-role of tetrahydrobiopterin. *FEBS Lett*. 1990;277:215–9.
 220. Schmidt HH, Pollock JS, Nakane M, Gorsky LD, Forstermann U, Murad F. Purification of a soluble isoform of guanylyl cyclase-activating-factor synthase. *Proc Natl Acad Sci U S A*. 1991;88:365–9.
 221. Bredt DS, Snyder SH. Isolation of nitric oxide synthetase, a calmodulin-requiring enzyme. *Proc Natl Acad Sci U S A*. 1990;87:682–5.
 222. Chen J, Cui X, Zacharek A, Roberts C, Chopp M. eNOS mediates TO90317 treatment-induced angiogenesis and functional outcome after stroke in mice. *Stroke*. 2009;40:2532–8.
 223. Lee CZ, Xue Z, Hao Q, Yang GY, Young WL. Nitric oxide in vascular endothelial growth factor-induced focal angiogenesis and matrix metalloproteinase-9 activity in the mouse brain. *Stroke*. 2009;40:2879–81.
 224. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol*. 2007;7:678–89.
 225. Wittchen ES. Endothelial signaling in paracellular and transcellular leukocyte transmigration. *Front Biosci (Landmark Ed)*. 2009;14:2522–45.
 226. Dirx AE, Oude Egbrink MG, Wagstaff J, Griffioen AW. Monocyte/macrophage infiltration in tumors: modulators of angiogenesis. *J Leukoc Biol*. 2006;80:1183–96.
 227. Schlesinger M, Bendas G. Vascular cell adhesion molecule-1 (VCAM-1)—an increasing insight into its role in tumorigenicity and metastasis. *Int J Cancer*. 2015;136:2504–14.
 228. Koch AE, Halloran MM, Haskell CJ, Shah MR, Polverini PJ. Angiogenesis mediated by soluble forms of E-selectin and vascular cell adhesion molecule-1. *Nature*. 1995;376:517–9.
 229. Kurland DB, Tosun C, Pampori A, Karimy JK, Caffes NM, Gerzanich V, et al. Glibenclamide for the treatment of acute CNS injury. *Pharmaceuticals (Basel)*. 2013;6:1287–303.
 230. Vasa M, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, et al. Number and migratory activity of circulating endothelial

- progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res*. 2001;89:E1–7.
231. Ding G, Jiang Q, Li L, Zhang L, Zhang ZG, Ledbetter KA, et al. Magnetic resonance imaging investigation of axonal remodeling and angiogenesis after embolic stroke in sildenafil-treated rats. *J Cereb Blood Flow Metab*. 2008;28:1440–8.
 232. Li L, Jiang Q, Zhang L, Ding G, Gang Zhang Z, Li Q, et al. Angiogenesis and improved cerebral blood flow in the ischemic boundary area detected by MRI after administration of sildenafil to rats with embolic stroke. *Brain Res*. 2007;1132:185–92.
 233. Zhang R, Wang Y, Zhang L, Zhang Z, Tsang W, Lu M, et al. Sildenafil (Viagra) induces neurogenesis and promotes functional recovery after stroke in rats. *Stroke*. 2002;33:2675–80.
 234. Grammas P, Martinez J, Sanchez A, Yin X, Riley J, Gay D, et al. A new paradigm for the treatment of Alzheimer's disease: targeting vascular activation. *J Alzheimers Dis*. 2014;40:619–30.
 235. Guo XB, Deng X, Wei Y. Homing of cultured endothelial progenitor cells and their effect on traumatic brain injury in rat model. *Sci Rep*. 2017;7:4164.
 236. Huang XT, Zhang YQ, Li SJ, Li SH, Tang Q, Wang ZT, et al. Intracerebroventricular transplantation of ex vivo expanded endothelial colony-forming cells restores blood-brain barrier integrity and promotes angiogenesis of mice with traumatic brain injury. *J Neurotrauma*. 2013;30:2080–8.
 237. Li Z, Xiao J, Xu X, Li W, Zhong R, Qi L, et al. M-CSF, IL-6, and TGF- β promote generation of a new subset of tissue repair macrophage for traumatic brain injury recovery. *Sci Adv*. 2021;7:eabb6260. <https://doi.org/10.1126/sciadv.abb6260>.
 238. Lu J, Guan F, Cui F, Sun X, Zhao L, Wang Y, et al. Enhanced angiogenesis by the hyaluronic acid hydrogels immobilized with a VEGF mimetic peptide in a traumatic brain injury model in rats. *Regen Biomater*. 2019;6:325–34.
 239. Thau-Zuchman O, Shohami E, Alexandrovich AG, Leker RR. Combination of vascular endothelial and fibroblast growth factor 2 for induction of neurogenesis and angiogenesis after traumatic brain injury. *J Mol Neurosci*. 2012;47:166–72.
 240. Gan ZS, Stein SC, Swanson R, Guan S, Garcia L, Mehta D, et al. Blood biomarkers for traumatic brain injury: a quantitative assessment of diagnostic and prognostic accuracy. *Front Neurol*. 2019;10:446.
 241. Zetterberg H, Blennow K. Fluid biomarkers for mild traumatic brain injury and related conditions. *Nat Rev Neurol*. 2016;12:563–74.
 242. Brouns R, Wauters A, De Surgeloose D, Marien P, De Deyn PP. Biochemical markers for blood-brain barrier dysfunction in acute ischemic stroke correlate with evolution and outcome. *Eur Neurol*. 2011;65:23–31.
 243. Cummins PM. Occludin: one protein, many forms. *Mol Cell Biol*. 2012;32:242–50.
 244. Baker TL, Agoston DV, Brady RD, Major B, McDonald SJ, Mychasiuk R, et al. Targeting the cerebrovascular system: next-generation biomarkers and treatment for mild traumatic brain injury. *Neuroscientist*. 2022;28:594–612.
 245. Battaglini D, Siwicki-Gieroba D, Rocco PR, Cruz FF, Silva PL, Dabrowski W, et al. Novel synthetic and natural therapies for traumatic brain injury. *Curr Neuropharmacol*. 2021;19:1661–87.