What Are the Roles of Pericytes in the Neurovascular Unit and Its Disorders?

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Pericytes are fundamental components of the neurovascular unit (NVU). They interact with endothelial cells, basal lamina (basement membrane), and glial cells and have a critical role in maintenance of blood-brain barrier (BBB) stability, local control of capillary blood flow, angiogenesis, and immune responses. Pericytes may also function as stem cells with potential to differentiate to into smooth muscle, glial cells, or neurons. A wide range on neurologic disorders, including vascular disorders, neurodegenerative disorders such as Alzheimer disease (AD), traumatic injury, and multiple sclerosis (MS) are associated with changes in pericyte structure and function affecting the NVU. Dysfunctional pericyte signaling may be a potential biomarker of NVU pathology and provides therapeutic targets for neuroprotection. The functions of pericytes and their role in neurologic disorders have been the subject of several comprehensive reviews.[1-13]

Development, Heterogeneity, and Dynamics of Pericytes

The NVU is a fundamental structural and functional unit in the CNS and includes endothelial cells, pericytes, vascular smooth muscle cells, basal lamina, astrocytes, microglia, and neurons (Figure).[14] The CNS has the highest density of pericytes compared with other tissues; about 70%–80% of microvessels are covered by pericytes.[15] Pericytes are contractile cells that are located between endothelial cells and other cells of the NVU and are almost entirely embedded within the basal lamina. Pericytes constitute a heterogeneous population from the standpoint of their origin, location, morphology, protein expression, and function.[16] Forebrain pericytes originate from neural crest cells, whereas those in the brainstem and spinal cord originate from mesenchymal stem cells.[4] During development, the newly formed capillaries attract pericytes by secreting platelet-derived growth factor (PDGF)-B, which binds to the PDGF receptor β (PDGFRβ).[17] The expression of PGDRβ in pericytes depends on their integrin-mediated adhesion to laminin in the basal lamina.[4] Pericytes situated at different locations along capillaries have different morphology. Precapillary pericytes have many circumferential processes that wrap around blood vessels; midcapillary pericytes are long, spindle-shaped cells that extend processes parallel to the length of microvessels, and postcapillary pericytes are short stellate-shaped cells that cover the abluminal surface of postcapillaries and postcapillary venules.[18] Pericytes express several molecular markers that vary across different tissues, locations within the vascular tree, developmental state, and pathologic setting.[4,16] Common markers include PGDRβ, α-smooth muscle actin, and potassium channel Kir6.1. Adhesion between pericytes and endothelial cells is promoted by transforming growth factor-β (TGF-β) secreted from both cell types in a paracrine and autocrine manner.[19] TGF-β also upregulates expression of α-smooth muscle actin, which is the primary contractile protein in pericytes.[19] Pericytes may also express vascular cell adhesion molecule (V-CAM) and immunologic markers such as Fc receptor, CD4, CD11b, and major histocompatibility complex (MHC) Class I and II molecules among other markers.[5,20,21] In mature adult brains, pericytes residing in a stable microvessel network are relatively quiescent with a low rate of turnover. Both physiologic conditions that require expansion of the vasculature, such as increased metabolic activity, or pathologic conditions such as hypoxia and inflammation trigger pericyte activation, proliferation, self-renewal, and differentiation. Pathologic insults can both increase the proliferation of pericytes in

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Glossary

ACE2 = angiotensin-converting enzyme 2; **AD** = Alzheimer disease; **AQP-4** = aquaporin-4; **ATP** = adenosine triphosphate; **BBB** = blood-brain barrier; **BMP** = bone morphogenetic protein; **Ca^{2+}** = calcium; **CCM** = cerebral cavernous malformation; **ECM** = extracellular matrix; **Htra1** = high temperature requirement A1; **MHC** = major histocompatibility complex; **MMP** = metalloproteinase; **MS** = multiple sclerosis; **NO** = nitric oxide; **NVU** = neurovascular unit; **PDGF** = platelet-derived growth factor; **PDGFRβ** = PDGF receptor β; **ROS** = reactive oxygen species; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **TGF-β** = transforming growth factor-β; **TIMP-3** = tissue inhibitor of MMP-3; **TNF-α** = tumor necrosis factor-α; **V-CAM** = vascular cell adhesion molecule; **VEGF** = vascular endothelial growth factor.

preexisting pools around brain vessels and recruit pericyte progenitor cells from the bone marrow.[6] In culture, pericytes can behave as multipotential stem cells that can differentiate into multiple lineages, including smooth muscle cells, oligodendrocyte precursor cells, microglia, and neurons.[5,22-25] Maintenance of the self-renewal and multipotent state of pericytes depends on their interactions with laminin secreted by astrocytes.[26] However, the differentiation potential of pericytes varies according to the specific tissue[27] and is epigenetically regulated, for example, by tissue-specific histone modification patterns.[28]

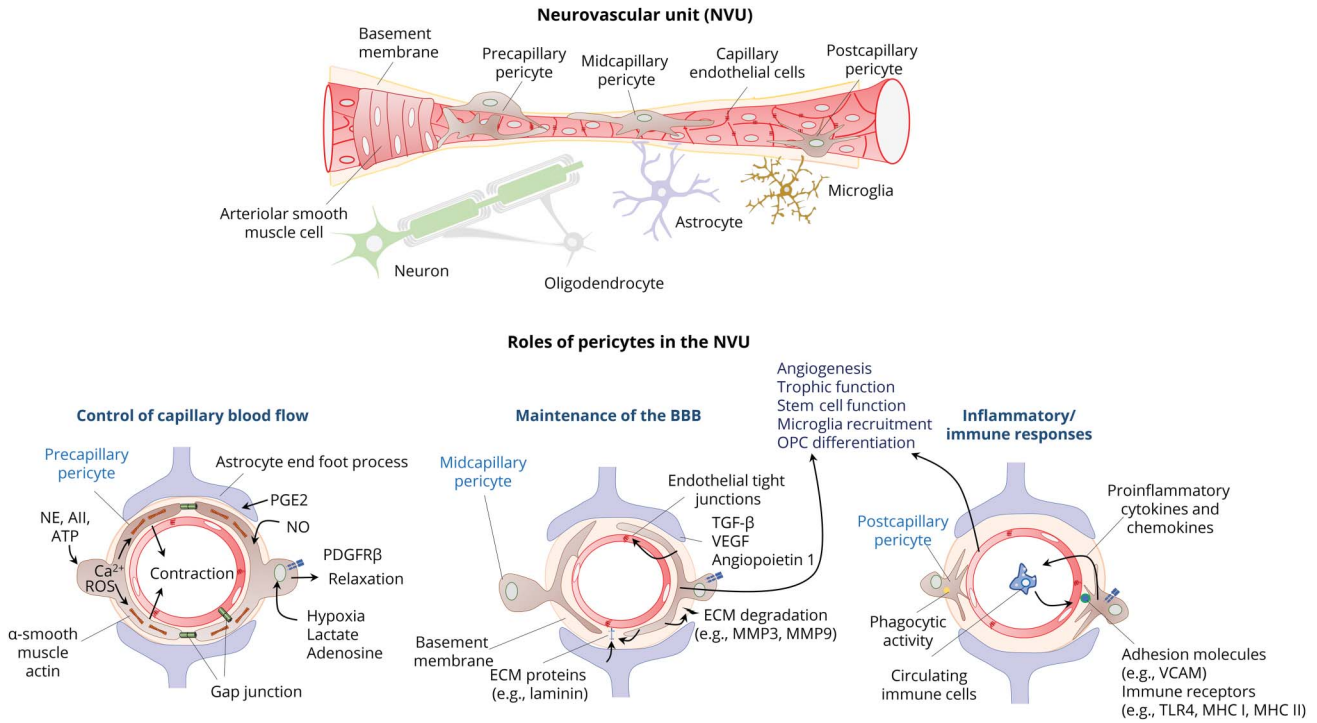
Functions of Pericytes in the NVU

Pericytes have several fundamental roles in the NVU, including maintenance of the BBB, regulation of capillary flow, paracrine interactions with other cells regulating angiogenesis, and survival, phagocytosis, and inflammatory responses.[3,6,7,13,29-32] Pericytes extend processes that preferentially wrap around tight junctions between neighboring endothelial cells forming the BBB[33-35] and the blood-retina barrier.[36] The basement membrane separating pericytes and endothelial cells has hole-like structures that allow endothelial cell–pericyte communication and interactions via gap and adhesion junctions. These close interactions enable pericytes to provide structural and nutritional support to endothelial cells to enhance the barrier function of the BBB.[37-39] For example, pericytes secrete angiopoietin 1, which induces tight junction formation between endothelial cells.[40,41] Pericytes participate in the formation and degradation of extracellular matrix (ECM) proteins of the basement membrane. This special form of matrisome surrounds the cerebral microvessels at the interface between endothelial cells, contractile cells (smooth muscle cells and pericytes), and astrocyte endfeet.[42,43] Pericytes, like endothelial cells and astrocytes, synthesize laminin, collagen IV, nidogen, and perlecan, which are the main ECM proteins of the basement membrane.[41,42] The production of ECM proteins by pericytes is stimulated by TGF-β, which leads to upregulation of cadherin-2 and tight junction stabilization in cerebral endothelial cells.[3] Pericytes also produce metalloproteinase (MMP)-2 and MMP-9, which enhance ECM degradation during early stages of angiogenesis. However, they also produce tissue inhibitor of MMP-3 (TIMP-3), which facilitates vessel maturation and stabilization.[44,45] Pericytes function synergically with astrocytes to maintain the normal function of the BBB.[46-48] For example, astrocytes release laminin, which binds to integrin α2 on pericytes and maintains pericytes in a BBB stabilizing status preventing them from switching to a contractile status.[26] Pericytes regulate the polarization of aquaporin-4 (AQP-4) to the perivascular astrocytic end foot membrane.[49]

In addition to their fundamental structural functions, pericytes have a major role in the regulation of local cerebral blood flow. Ensheathing pericytes at the arteriole-capillary transitional zone, like arteriolar smooth muscle cells, control large-scale, rapid changes in blood flow, whereas capillary pericytes act on slower and smaller scales and control resting capillary tone and flow heterogeneity according to local demands.[31,50,51] Pericytes contain contractile proteins such as α-smooth muscle actin, tropomyosin, and desmin.[51] This allows pericytes to bidirectionally regulate blood flow depending on neuronal activity, metabolic state, and neurotransmitter signals resulting in changes in intracellular calcium (Ca^{2+}).[52,53] Ensheathing pericytes at the arteriole-capillary transition zone express the highest levels of α-smooth muscle actin and exhibit highly regular oscillatory Ca^{2+} fluctuations compared with capillary and perivenular pericytes and thus have the primary responsible for regulation of microvascular blood flow.[54] Adjoining membranes of neighboring pericytes are interconnected via gap junctions, which allow them to function as a syncytium along the microvascular wall.[32,52] Propagation of vasomotor responses in response to local changes of neural activity also depends on connexin-43 gap junctions between pericytes and endothelial cells.[55,56]

In physiologic conditions, pericytes contribute to neurovascular coupling by contracting or relaxing according to the energy demands of nervous tissue. Pericyte-mediated capillary dilation occurs before arteriolar dilation in response to a focal increase in energy demand from a small group of nearby neural cells.[32] In contrast, regional blood flow is primarily controlled by arteriolar smooth muscle contractility.[57] Several mediators, including neurotransmitters, PDGF-β, adenosine triphosphate (ATP), adenosine, and nitric oxide (NO), control pericyte contractility. For example, glutamate released during excitatory synaptic activity promotes pericyte relaxation and capillary vasodilation via a mechanism that involves NO and prostaglandin E2.[58] PDGF-β can activate nonspecific cation channels, chloride channels, and ATP-

Figure Components of the NVU and Roles of Pericytes



The neurovascular unit (NVU) includes endothelial cells, pericytes, vascular smooth muscle cells, basal lamina (or basement membrane), astrocytes, microglia, and neurons. Pericytes are located between endothelial cells and other cells of the NVU and are embedded within the basal lamina. Newly formed capillaries attract pericytes by secreting platelet-derived growth factor (PDGF)-B, which binds to the PDGF receptor β (PDGFRβ) in pericytes. Precapillary pericytes wrap around blood vessels and express high levels of α-smooth muscle actin, which allows them to bidirectionally regulate blood flow in response to signals that elicit changes in intracellular calcium (Ca^{2+}). Gap junctions between pericytes with each other and with endothelial allow propagation of vasomotor responses. Glutamatergic synaptic activity promotes pericyte relaxation and capillary vasodilation by activating production of nitric oxide (NO) and prostaglandin E2 (PgE2) in synaptic terminal and astrocytes, respectively. Hypoxia, lactate, and adenosine can also relax pericytes. In contrast, adenosine triphosphate (ATP), norepinephrine (NE) angiotensin II (AII), and accumulation of intracellular reactive oxygen species (ROS) promote pericyte contraction. Midcapillary pericytes have a major role in maintenance of the blood-brain barrier (BBB). They secrete transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and angiopoietin 1, which induces tight junction formation and promote angiogenesis. Pericytes participate in the formation and degradation of extracellular matrix (ECM) proteins of the basement membrane. They synthesize ECM proteins such as laminin and also produce metalloproteinase (MMP)-2 and MMP-9, which enhance ECM degradation. Pericytes express vascular cell adhesion molecule (V-CAM) and immune receptors such as Toll-like receptor 4 (TLR4), and major histocompatibility complex (MHC) molecules I and II have phagocytic activity, secrete proinflammatory cytokines and chemokines, and attract immune cells from the bloodstream. In response to microenvironmental changes, pericytes secrete different molecules that function as paracrine signals including growth factors that regulate differentiation of various progenitors in the neurovascular unit. Pericytes may also behave as multipotential stem cells that can differentiate into multiple lineages, including smooth muscle cells, oligodendrocyte precursor cells, microglia, and neurons.

sensitive potassium channels to regulate contractility of pericytes according to the metabolic status. Signals of increased energy consumption, such as hypoxia, lactate, adenosine, low pH, and transient elevation of reactive oxygen species (ROS), can also relax pericytes.[31,59] In contrast, increased levels of ATP induce pericyte contraction via P2X7 receptors.[60] Pericytes also respond to vasoactive substances such as norepinephrine[61] and angiotensin II.[62] They express angiotensin-converting enzyme 2 (ACE2), which converts vasoconstricting angiotensin II into vasodilating angiotensin-(1-7).[62] The proportion of microvascular pericytes that are able to contract varies depending on the tissue, species, developmental stage, and localization along the arteriovenous length.[63]

In response to microenvironmental changes, pericytes may also secrete different molecules that function as paracrine signals. The pericyte secretome is both tissue and stimulus specific and includes growth factors, ECM proteins, and pro- and anti-inflammatory cytokines.[64] Some pericyte signals regulate cell survival and differentiation within the NVU.[65] For example, pericytes release vascular endothelial growth factor (VEGF), angiopoietin 1, and other signals that promote angiogenesis.[8] Angiopoietin 1 and glial-derived neurotrophic factor enhance tight junction formation,[66] whereas VEGF and TGF-β1 protect endothelial cells.[19,67] Pericytes also provide trophic factors for glial cells and neurons.[38,68] For example, pericytes contact oligodendrocyte precursor cells, and both cell populations reciprocally regulate their proliferation and survival.[65,69,70] Pericytes induce the differentiation of new oligodendrocytes from precursor cells by secreting laminin alpha2 chain in the microvascular basal lamina, thus promoting myelin development.[68,70-72]

Pericytes are involved in inflammatory and immune responses at the NVU.[73] They express pattern recognition receptors

such as Toll-like receptor 4 and Fc receptors, may develop macrophage-like phagocytotic ability, and contain cytoplasmic lysosome-like granules; this indicates that they recognize abnormal antigens and serve as scavenger cells.[74] Pericytes also express adhesion molecules that promote leukocyte recruitment, may secrete proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interferon-gamma, and produce ROS, NO, and other inflammatory mediators during immune reactions.[5,29,38,75-77] Perivenular pericytes may have major role in regulating peripheral immune cells infiltration in response to insults affecting the NVU.[7] However, in some conditions, pericytes may inhibit proliferation and cytokine production of activated T cells, thus protecting endothelial cells from inflammation-mediated apoptosis.[78] This indicates that in physiologic conditions, pericytes could prevent unnecessary immune reactions, while in response to injury cells, they can readily initiate inflammatory responses.

Clinical Correlations

Animal models show that pericyte loss or dysfunction is associated with BBB impairment, microaneurysms, and endothelial cell hyperplasia.[2,35,61,79] Pericytes may be affected by aging and in a wide variety of neurologic disorders.[8,10,13,80] Studies on the effects of aging on pericyte number and BBB function have provided contradictory results.[2,81,82] However, with aging, pericytes may accumulate vacuolar inclusions and show increased expression of α-smooth muscle actin, altered length and orientation of desmin filaments, and reduced contacts with endothelial cells.[83,84] Whereas accumulation of vacuolar inclusions may reflect phagocytotic activity as a defense against potential BBB leakage,[83] changes desmin filaments can reflect pericyte sclerosis with resultant impairment of their capacity to regulate local blood flow.[2] Several factors, including oxidative stress, may contribute to pericyte dysfunction during aging.[85] Hyperlipidemia,[67] diabetes mellitus,[86] and hypertension[87] may all affect pericyte function. The role of pericytes in neurologic disorders has been extensively reviewed,[8-13,78,88-95] and only few concepts will be emphasized here.

Cerebral Ischemia

Pericytes are among the first cell types that react to brain hypoxia-ischemia and participate in various compensatory, pathologic, and repair processes during ischemic stroke.[8] These changes may have either beneficial or deleterious effects according to the timing and severity of the insult. For example, studies in experimental models show that during short-duration ischemia, pericytes relax in response to increased levels of PDGF-β, adenosine, and NO.[59,88] However, during sustained ischemia, pericyte reverse their phenotype to produce constriction in response to ROS and peroxynitrite generated during ischemia and reperfusion[87]; this contributes to the non-reflow phenomenon after ischemic stroke.[53] In this setting, pericytes constrict capillaries through a Ca^{2+}-induced α-smooth muscle actin contraction and subsequently die due to an uncontrolled overload of intracellular Ca^{2+} potentiated by ROS generated by pericyte mitochondria, endothelial cells, and astrocyte endfeet.[96,97]

Pericytes may also have a protective or deleterious effect on the maintenance of BBB integrity in the setting of ischemia. In response to PDGF signaling, pericytes change from a quiescent flat into an ameboid morphology, separate from the basal lamina, and migrate toward the hypoperfused area. This migration may be protective as pericytes can release trophic factors such as VEGF, angiopoietin 1, glial-derived neurotrophic factor, and TGF-β1, which promote angiogenesis and maintain BBB integrity, as well as other neuroprotective factors for other cellular components of the NVU.[8,19,38,66,68,89,98] Pericytes may also exert neuroprotective effects by adopting phagocytic activity and functioning as multipotential stem cells that generate microglia, thus contributing to clearance of tissue debris thereby alleviating local inflammation and reducing secondary tissue damage.[90,99] Accumulation of oxygen free radicals promotes nuclear factor erythroid-2–related factor 2 signaling in pericytes, allowing them to acquire stem-like characteristics.[100] However, pericytes may not be able to reconstruct a functional NVU and rather contribute to formation of a glial scar under pathologic conditions.[101]

Pericytes may also participate in deleterious responses in the setting of ischemia. They express nicotinamide adenine dinucleotide phosphate oxidase, which is upregulated in the peri-infarct region and generates superoxide, promoting MMP-9 release resulting in disruption of the BBB.[30,102-104] Furthermore, MMP-9, bone morphogenetic protein (BMP)-4, and endostatin-1 secreted by pericytes may inhibit angiogenesis.[105,106] Ischemic injury can be aggravated by inflammatory responses due to recruitment and transmigration of immune cells to ischemic or peri-ischemic tissue.[107] Pericytes express intercellular adhesion molecule 1,[108] which interacts with integrins on leukocytes to guide leukocyte migration.[109]

Small Vessel Disease

Pericytes may have a role in small vessel disease associated with disorders of the matrisome.[43] A common mechanism in several of these disorders is disturbed TGF-β signaling.[110] As mentioned earlier in this review, TGF-β mediates numerous cellular processes including pericyte and endothelial cell proliferation, differentiation, and vascular remodeling. This cytokine is secreted by both pericytes and endothelial cells as a proform that needs activation by proteases, thrombospondin, or integrins.[111] In basal conditions, mature TGF-β is kept in a functionally inactive state by forming a complex with latent TGF-β–binding protein 1 that is anchored to the ECM.[112] Latent TGF-β–binding protein 1 is a substrate of the high temperature requirement A1 (Htra1) serine protease/peptidase

encoded by the *HTRA1* gene. Activated TGF-β acts via 2 types of receptors, both of which are expressed in pericytes and elicit distinct intracellular transcription factor cascades that promote vessel maturation, inhibit pericyte proliferation, and induce upregulation of expression of contractile proteins.[113] The recruitment and proper attachment of pericytes to endothelial cells leads to activation of secreted TGF-β signaling, promoting VGEF receptor expression and differentiation of endothelial cells, inhibition of their proliferation, and formation and stabilization of the basement membrane and BBB.[113] Knockouts of many of the proteins involved in this signaling pathway lead to severe vascular abnormalities.[3] Pathogenic *HTRA1* variants leading to reduced enzymatic activity are associated with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.[91] These variants reduce TGF-β release from its complex with TGF–β binding protein 1 but also increase levels of TGF-β, as it is a substrate of the serine protease encoded by *HTRA1*.[114] Thus, the precise mechanisms by which *HTRA1* variants affect TGF-β signaling in the microvasculature are still incompletely defined.[92] A postmortem study in brains of patients with acquired small vessel disease showed high expression of BMP-4, a member of the *TGFB* superfamily in white matter pericytes; this was associated with increased angiogenesis and astrogliogenesis at the expense of oligodendrocyte precursor cell proliferation and maturation, thereby aggravating white matter damage.[115] Pericytes may also be involved in the vascular complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[116] SARS-CoV-2 binding removes ACE2 from the cell surface membrane and thus impairs conversion of angiotensin II to angiotensin-(1-7)[62] leading pericyte-mediated angiotensin II evoked cerebral capillary constriction.[116]

Familial Cerebral Cavernous Malformations

Familial cerebral cavernous malformation (CCM) is caused by loss-of-function variants in *CCM1*, *CCM2*, or *CCM3* genes in endothelial cells and consists of multiple, dilated capillary channels formed by a single layer of endothelium and lacking parenchymal cells. Given the ubiquitous expression of CCM proteins, it is not known why CCM lesions are confined to the brain.[93] Whereas the primary defect in CCMs is thought to be intrinsic to endothelial cells, recent evidence indicates a contribution of pericyte dysfunction. For example, studies in experimental models indicate that Ccm3 deletion in pericytes also induces CCM lesions by destabilizing pericyte–endothelial cell interactions.[93] Pericytes in Ccm1 knockout mice have increased expression of PDGFRβ and ECM genes, particularly that encoding fibronectin-1; human CCM lesions had abundant fibronectin deposition in pericytes.[117]

Alzheimer Disease

Disturbances of the NVU, including structural alterations of the brain capillaries, impaired control of microcirculation, and disruption of the BBB are well-recognized features of AD.[14,94,95,118-122] Involvement of pericytes is particularly relevant given their key role in microvascular stability, capillary density, and angiogenesis.[80,118,123,124] For example, β-amyloid targets pericytes, eliciting vasoconstriction and disrupting capillary blood flow.[11,12] Cerebrovascular pericytes acting together with perivascular astroglial cells have also been implicated in the production of lipidated, reactive forms of ApoE, which in turn suppresses pericyte motility and adhesion to endothelial cells.[125] Dysfunctional microvascular pericytes release soluble PDGFRβ, which has been proposed as a biomarker of BBB integrity and predictor of neurodegeneration.[126]

Multiple Sclerosis

Studies in experimental models and in postmortem brain tissues of patients with MS show that pericytes and other perivascular cell populations have different behavior depending on the lesion type and clinical course of the disease.[127] Active lesions contain higher numbers of proliferative perivascular cells than inactive lesions, whereas chronic lesions have lower numbers of proliferative perivascular cells than normal-appearing white matter.[127] In experimental allergic encephalomyelitis, oligodendrocyte precursor cells make more contacts with pericytes leading to tight junction impairment and BBB leakage.[71,128,129] Activation of P2X7 receptors by ATP released during inflammation leads to downregulation of both PDGFRβ in pericytes and claudin-5 in endothelial cells also leading to BBB disruption.[130] Pericytes may also contribute to neuroinflammation in MS by their ability to secrete adhesion molecules, chemokines, and cytokines that assist in the recruitment and migration of immune cells.[75-77,131] As shown in traumatic injury models, microglial-released TNF-α initiates a nuclear factor kappa B pathway–inducible NO synthase cascade that results in pericyte damage.[132]

Perspective

As a fundamental component of the NVU, pericytes have a major role in preserving the neural microenvironment. Their dysfunction leads to BBB disruption, disturbed local blood flow, and neuroinflammation. Pericytes thus provide a major potential target for neuroprotection. Treatments targeting hyperlipidemia, diabetes, or hypertension may be beneficial in ischemic injury or neurodegeneration in part by protecting pericytes. In preclinical studies, some drugs affecting pericytes may be neuroprotective against ischemic injury. For example, in spontaneously hypertensive rats, the antiplatelet drug cilostazol prevented the detachment of pericytes from microvessels and enhanced pericyte proliferation while inhibiting production of MMP-9.[133] A study showed that short-term treatment with cilostazol and isosorbide mononitrate, alone or in combination, improved MRI-measured cerebrovascular function in patients with lacunar stroke.[134] In experimental

models, the free radical scavenger edaravone also promoted pericyte proliferation, increased pericyte coverage of endothelial cells, and reduced production of MMP-9, thus attenuating BBB destruction during reperfusion injury.[135] However, these drugs also affect other cells of the NVU besides pericytes. Furthermore, these promising results may not be reproducible in clinical conditions, given the functional heterogeneity of pericytes and their varying and sometimes opposite responses depending on the environmental context, timing of injury, and other variables. Identification of specific molecular biomarkers may allow more precise targeting of pericytes as a major tool to protect NVU integrity in pathologic conditions.

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