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A role for pericytes in chronic pain?

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Abstract

Purpose of the review—The importance of the blood-brain barrier and neuroinflammation in neurodegenerative conditions is becoming increasingly apparent, yet very little is known about these neurovascular functions in non-malignant disease chronic pain. Neural tissue pericytes play critical roles in the formation and maintenance of the blood-brain barrier. Herein we review the important roles of neural pericytes and address their potential role in chronic pain.

Recent findings—Pericytes are implicated in the function of neural microvasculature, including blood-brain barrier permeability, neuroimmune factor secretion and leukocyte transmigration. In addition, the multipotent stem cell nature of pericytes affords pericytes the ability to migrate into neural parenchyma and differentiate into pain-associated cell-types. These recent findings indicate pericytes are key players in pathological blood-brain barrier disruption and neuroinflammation, and as such pericytes may be key players in chronic pain states.

Summary—Pericytes play key roles in pathological processes associated with chronic pain. We propose pericytes may be a therapeutic target for painful diseases that have associated neural vascular dysfunction. Given the paucity of new pharmacotherapies for chronic pain conditions we hope that this review inspires researchers to unearth the potential role(s) of pericytes in chronic pain sowing the seeds for future new chronic pain therapies.

Keywords

Pericytes; vascular dysfunction; blood-brain barrier; chronic pain

2 Introduction

The financial burden of treating chronic non-malignant pain is ever increasing in our ageing global population. There has been a paucity of new pharmacotherapies for chronic non-malignant pain despite increased attention from researchers and clinicians in areas such as musculoskeletal and neuropathic pain. Over the last four decades the number of published research articles focussing on chronic pain has risen exponentially yet the number of new therapeutics to treat chronic pain have not risen in tandem, leaving an over-reliance on the old pharmacological classes: opioids, anticonvulsants, anti-depressants and non-steroidal

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Conflicts of interest
None to declare

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anti-inflammatory drugs(1). Identifying new targets is key to driving progress in pharmacotherapy of disease. The importance of the neurovascular unit (NVU) and blood-brain barrier (BBB) in neurodegenerative conditions is becoming increasingly apparent yet the potential role(s) of the NVU and BBB in the development and maintenance of chronic pain is/are significantly under researched and could provide new avenues for the treatment of chronic pain conditions. Pericytes are a key component of vascular barrier function. Herein we review the critical role pericytes play in the BBB and how pericyte (dys)function may contribute to the persistent pain states thereby presenting a novel target in the pharmacotherapy of chronic pain in non-malignant disease.

2.1 Pericytes in the blood-brain barrier

The BBB and blood-spinal cord barriers (BSCB) restrict access of potentially harmful cells, molecules and other agents into the central nervous system (CNS) and maintain an appropriate microenvironment for neuronal homeostasis. The multicellular makeup of the CNS microvasculature is composed of unfenestrated and tightly connected endothelial cells, pericytes and perivascular immune cells residing in the basement membrane, vascular-associated microglia and astrocytic end-feet. Neural tissue contains the highest ratio of pericytes to endothelial cells, with pericytes living within the basement membrane of pre-capillary arterioles, capillaries and post-capillary venuoles and encircling the endothelium with finger-like projections(2). Astrocytic end-feet encase the basement membrane and form another barrier, the glia limitans. The permeability of the BBB in both development and adulthood inversely correlates with pericyte coverage(3, 4) and in the spinal cord pericyte capillary coverage is reduced in comparison to the brain, which correlates with increased barrier permeability and lower expression of tight junction proteins, zonula occludens-1 (ZO-1) and occludin(5). These indicate an important role for pericytes in maintaining CNS barrier integrity.

2.2 Pericytes in neuroinflammation

Neuroinflammation is a common symptom in pathophysiological conditions including systemic inflammation, diabetes, stroke, multiple sclerosis and chronic pain conditions(6, 7). In neuroinflammatory conditions, the BBB and BSCB are disrupted, facilitating entry of blood-borne molecules and cells into the CNS that affect the neural microenvironment(8). In preclinical painful neuropathy models the BBB/BSCB is altered(9–13). Many blood-derived molecules are neurotoxic and can cause neuronal sensitization (for example, erythrocytic free iron, fibrinogen, plasminogen and thrombin) therefore extravasation of blood-borne molecules in chronic painful conditions with an neuroinflammatory component may contribute to an increased pain state. Most research into CNS barrier disruption has focussed on endothelial, glial, and neuronal signalling yet pericyte function is altered in pathophysiological conditions(14, 15), and because of their close proximity to endothelial cells and their intimate role in the NVU, they have the potential to directly perturb barrier function and permeability. As such there is great interest in the mechanisms by which pericytes stimulate inflammatory cytokine release and the consequent effects on the endothelium(16). Pericytes can release a host of factors involved in inflammation when exposed to pro-inflammatory substances, such as interleukins, chemokines and adhesion molecules(17, 18), and have been implicated in the promotion of immune cell

transendothelial migration (transmigration)(19, 20). Pericytes are more sensitive to TNFα stimulation, with an increased expression of inflammatory molecules and a larger migratory response compared to other cells of the neurovascular unit(21, 22). Furthermore, pericytes are able to induce greater microglial iNOS and IL-1β expression than astrocytes or endothelial cells(21) and produce more matrix metalloproteinase-9 (MMP-9) in response to thrombin stimulation(23, 24). Therefore, in addition to directly altering barrier function through inflammatory cytokine release, pericytes are able to activate glial cells which can exacerbate the inflammatory response and alter barrier function further(25). In painful conditions with a neuroinflammatory component, pericytes could be a key driver of prolonged neuroinflammation and barrier disruption (for review see(26)). There are numerous immune and growth factors that pericytes express which are also implicated in nociception and pain states (see Table 1 for a summary).

A recent study found in a model of peripheral neuropathy (chronic constriction injury: CCI) that the number of vascular platelet-derived growth factor- receptor-β^+ (PDGFR-β) and $CD13^+$ cells (pericytes) was reduced in the spinal cord and that there was a reduction in the tight-junction protein (TJP) expression(61), supporting an important role of pericyte function in peripherally driven CNS changes and the development of pain.

MMP production can contribute to neuroinflammation, activate glial cells, and can disrupt barrier integrity by degrading the basement membrane and tight junction proteins, and initiate pericyte migration and leukocyte transmigration(22, 62, 63). MMPs can also trigger VEGF-A production in endothelial cells, which is a potent permeability inducer(64) and a neuronal sensitizer(13, 54). Pericytes could be a key source of MMP-9 and VEGF-A in pathological conditions. Their close relationship with endothelial cells allows pericytic MMPs to directly act on endothelial tight junctions leading to pathological barrier disruptions(65). MMPs have been implicated in neuropathic pain(66, 67), but pericytes as a possible source have not been investigated.

Laminins are the most abundant non-collagenous protein in the basement membrane and are produced by astrocytes, endothelial cells, and pericytes(68). Mice that lack pericyte-derived laminin exhibit hydrocephalus, increased barrier permeability and reduced tight junction expression(68). Additionally, astrocytic function is altered. This demonstrates that pericytes actively contribute towards a physiological basement membrane, and disruption of pericytic-derived laminin can have significant consequences on barrier viability. Pericytes also contribute to remodelling of the basement membrane and facilitate leukocyte transmigration during acute inflammation(69), but the mechanisms of this are still unclear.

2.3 Pericytes in CNS immune infiltration

The CNS, once thought to be an immune-privileged site is now understood to be neither passive nor isolated from the peripheral immune system with highly regulated movement of leukocytes in and out of the neuronal parenchyma with glia and neurons regulating leukocyte responses (reviewed by(26)). In addition to barrier disruption pericytic cytokine secretion may contribute to leukocyte chemoattraction and infiltration into the CNS. Leukocytes target inter-pericytic gaps to transmigrate through the basement membrane and in inflammatory conditions these gaps are both increased in size and number as pericyte

morphology and coverage change, in response to inflammatory cytokines such TNFα and various interleukins(18). There is evidence of leukocyte transmigration into the CNS in pre-clinical models of painful neuropathy (70–72) and that these cells contribute to pain processing. In the non-malignant painful disease diabetes mellitus, hyperglycaemia results in oxidative stress and pericyte death in the peripheral nervous system (PNS), reducing endoneurial vessel coverage. Endoneurial vessels become more permeable to inflammatory agents including leukocytes(73), which possibly promotes inflammation-induced neuronal and Schwann cell apoptosis, contributing to the long-term pain associated with diabetic neuropathy(16).

Pericytic ICAM-1 is required for venular leukocyte migration within the basement membrane and finding gaps in the pericytic layer(74). Work from our laboratory has discovered peripheral inflammatory arthritis drives a CNS glio-vascular response with increased $GFAP^+$ astrocytic end-feet and microvascular ICAM-1 expression in the spinal cord of a pre-clinical model of inflammatory arthritis(75). Figure 1 displays an example of the observed ICAM-1^+ microvascular immunofluorescence detected in the dorsal horn of an arthritic subject which indicates the source of the ICAM-1 immunoreactivity is pericytic. This novel finding opens up many questions, for example are these ‘reactive pericytes’ promoting the transmigration of immune cells into the cord in response to the peripheral inflammatory reaction? Is the BSCB permeability increase in this model of peripheral inflammatory arthritis (72, 76) due to a pericytic reaction to nociceptive input from the inflamed joint? Our lab is attempting to answer these questions.

2.4 *In vitro* pericyte secretion

Whilst hyperglycaemic pericyte death and ensuing microvascular dysfunction in the PNS may be a pain-generating mechanism in diabetes mellitus, the aetiology of pericyte-related pain in inflammatory diseases may be more complex due to the convoluted nature of the cytokine profile secreted by endothelia in inflammatory environments(77). Due to the intricate interactions between tissues and these cytokines, identifying the molecules within these cascades *in vivo* is difficult to probe, thus novel methods need to be developed to investigate the inflammatory profile. One such method is a dynamic *in vitro* 3D BBB model that subjects co-cultures to haemodynamic forces and was designed as an alternative to existing static transwell models. Endothelial cells line an artificial lumen and are co-cultured with pericytes or astrocytes embedded in the surrounding collagen matrix(77). The authors stimulate the co-cultures with TNFα to measure the release of five pro-inflammatory molecules: granulocyte-colony stimulating factor (G-CSF); interleukin-6 (IL-6); IL-8; IL-17 and granulocyte-macrophage CSF; (77). Endothelial cells cultured in the presence of pericytes have an increase in both basal and TNFα-induced secretion of these cytokines, most notably IL-6 and IL-8, highlighting the ability of pericytes to enhance the neuroinflammation. Additionally basal G-CSF, a neuroprotectant[17], was detected when endothelial cells and pericytes were cultured together but not detected when endothelial cells were cultured alone [16]. This demonstrates the ability of pericytes to stimulate the production of a pro-neuronal factor which would be lost in pathological conditions associated with pericyte loss.

In chronic inflammation IL-6, IL-8, and TNFα are correlated with worsening prognoses and more severe levels of pathologies: increased levels of IL-6 have been linked to a series of severe polyneuropathies in addition to a number of painful diseases such as osteoarthritis(78–81). IL-8 has recently been found to be elevated in the cerebrospinal fluid of chronic pain state patients compared to controls and found to increase over time, correlating with sustained chronic pain(82). TNFα is increased in the CNS, joints and serum of patients with rheumatoid arthritis and other painful conditions(83–85). The pericytic secretion of nociceptive molecules induced by TNFα and other inflammatory mediators provides an additional mechanism by which pericytes may contribute to increased pain state, in addition to regulation of BBB and immune infiltration.

2.5 Targeting pericytes to promote delivery of analgesics

The selective BBB is a significant impediment for the delivery of therapeutics targeting CNS sensitisation and pain(86, 87). A reduction in pericyte coverage and tight junctions results in a more permeable BBB and despite the potential for increased noxious cytokine and cell infiltration into the CNS, this increased permeability could provide an opportunity for therapeutics to penetrate the BBB and reach their targets(88). However, although tight junctions such as ZO-1 and claudins represent a physical component of the BBB, it is the vast arsenal of efflux pumps that appear to present the biggest challenge to analgesic CNS therapy, as common opioids such as morphine operate transcellularly independent of paracellular barrier properties(89). The efflux pump p-glycoprotein is a key mediator in analgesic removal at the barrier. In a λ-carrageenan model of inflammatory pain, in which CNS tight junction proteins such as occludin are decreased, treatment with morphine and the NSAID diclofenac, a common combination to alter barrier permeability, was in fact found to upregulate p-glycoprotein expression in rats and lower morphine delivery to the CNS. Thus, despite changes in permeability, the delivery of analgesic therapy to the CNS can be governed by other factors, including upregulation of efflux transporters highly specific to drug substrates and drug-drug interactions(89). Nevertheless targeting pericytes to increase barrier permeability may improve the delivery of some analgesics into the CNS. In addition, P-glycoprotein is expressed by pericytes(90) yet the role of pericytes in analgesic efflux transporter activity is unknown and certainly worth pursuing.

2.6 Pericyte differentiation into a microglia-like phenotype

Pericytes can behave like mesenchymal stem cells being able to replace specialised cells such as adipocytes(91), myocytes(92), myofibroblasts(93) and odontoblasts(94) in repair processes. In response to CNS injury pericytes can migrate from the microvasculature into the neural parenchyma(95) and differentiate into a microglia-like phenotype(96–98), which may be a mechanism that contributes to increased pain. However it is not known if pericytic migration and differentiation occurs in vascular disrupted painful pathologies. If so this may present a novel mechanism to target in microglial associated neuroinflammation and neuronal sensitization known to underpin some chronic pain states, in preclinical models and in humans(99–102).

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3 Summary

The majority of research on pericyte and neural barrier change has focussed in stroke, neurodegeneration, and diabetes(16, 26, 103) without considering effects on nociception and pain states. Pericytes are essential for neural barrier formation and maintenance(4, 104) and reduced pericyte coverage correlates with increased permeability(5) but the specific mechanisms of pericytic function and neural barrier disruption are not known in chronic pain conditions that are associated with barrier disruption. There has been a small number of studies researching BSCB permeability in painful conditions such as nerve injury(103) and peripheral inflammation(105), demonstrating increased permeability and disrupted endothelial and barrier functioning, however pericytic involvement has been largely overlooked. Figure 2 summarises the key aspects of pericyte biology covered in this review that could lead to pain-generating mechanisms.

4 Conclusion

Due to the intimate relationship between pericytes and barrier health, pericytic dysfunction is likely to be present in painful pathologies that have associated neural tissue barrier disruption. Further research into pericyte biology in pain both in pre-clinical pain models and human studies may unearth pain-generating pericytic mechanisms, which would present novel therapeutic target(s) for the treatment of chronic pain.

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endothelial activation are involved in chronic pain which supports previous evidence from pre-clinical studies.]

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Key points

- Neurovascular dysregulation in chronic non-malignant pain conditions is currently under studied
- Pericytes are key for physiological neurovascular function
- Pericytes are intimately involved in neuroinflammatory processes associated with chronic pain conditions
- Neurovascular pericytic dysregulation and barrier disruption are observed in painful preclinical models of disease, and may be contributing factors to chronic pain
- Therefore, further research into pericytic dysregulation may reveal novel therapeutic targets for the treatment of chronic pain

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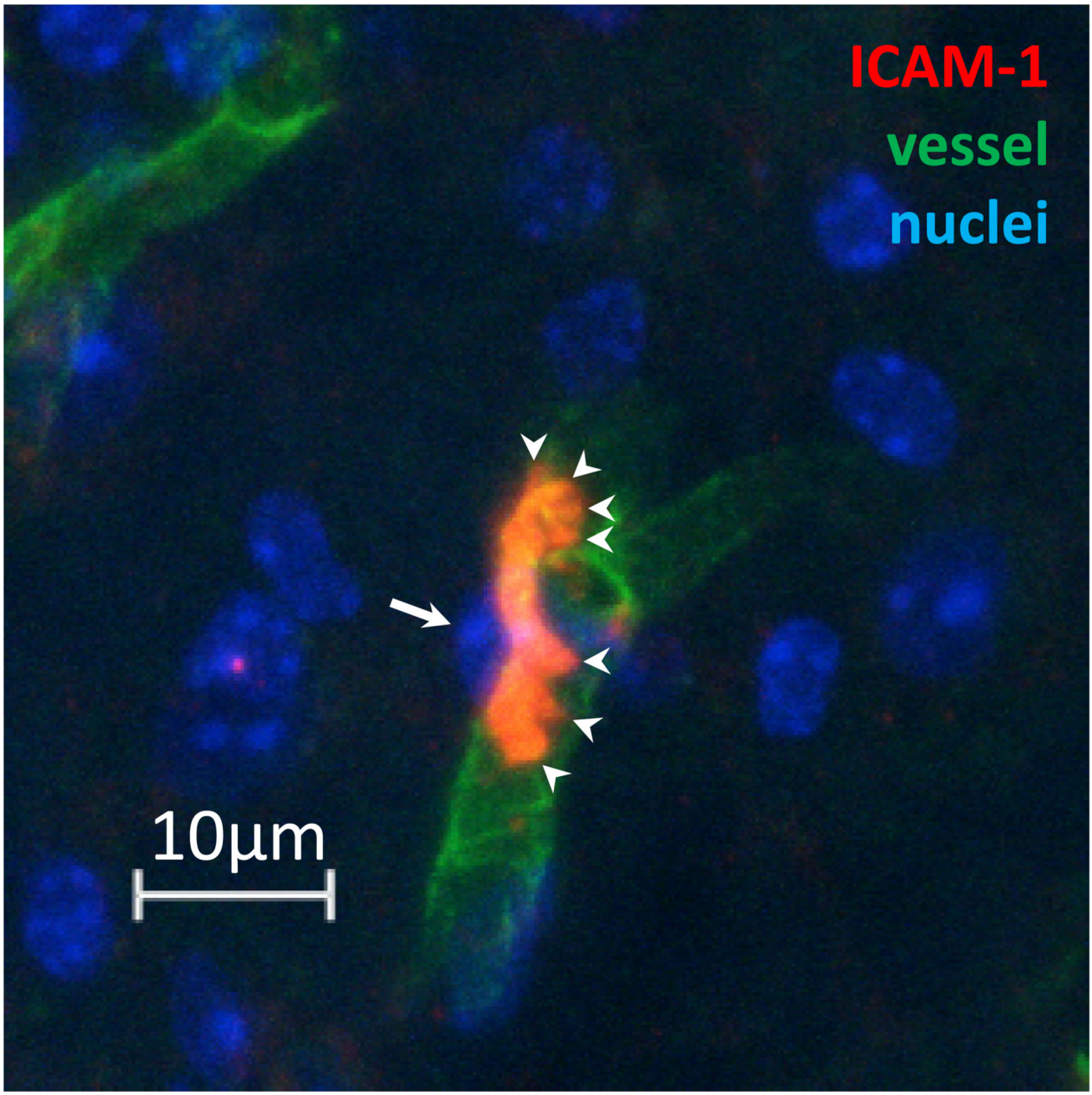

Figure 1.

CNS pericyte ICAM-1 expression is induced in a model of inflammatory pain. A representative ICAM-1^{+} pericyte in the dorsal horn of an inflammatory arthritic mouse. We have evidence that spinal cord pericytes are activated in a model of inflammatory arthritis indicating a CNS vascular response to peripheral inflammation. Arrow indicates cell nucleus or perivascular cell. Arrowhead indicate pericytic finger-like projection. Abbrev. ICAM-1 intercellular adhesion molecule-1.

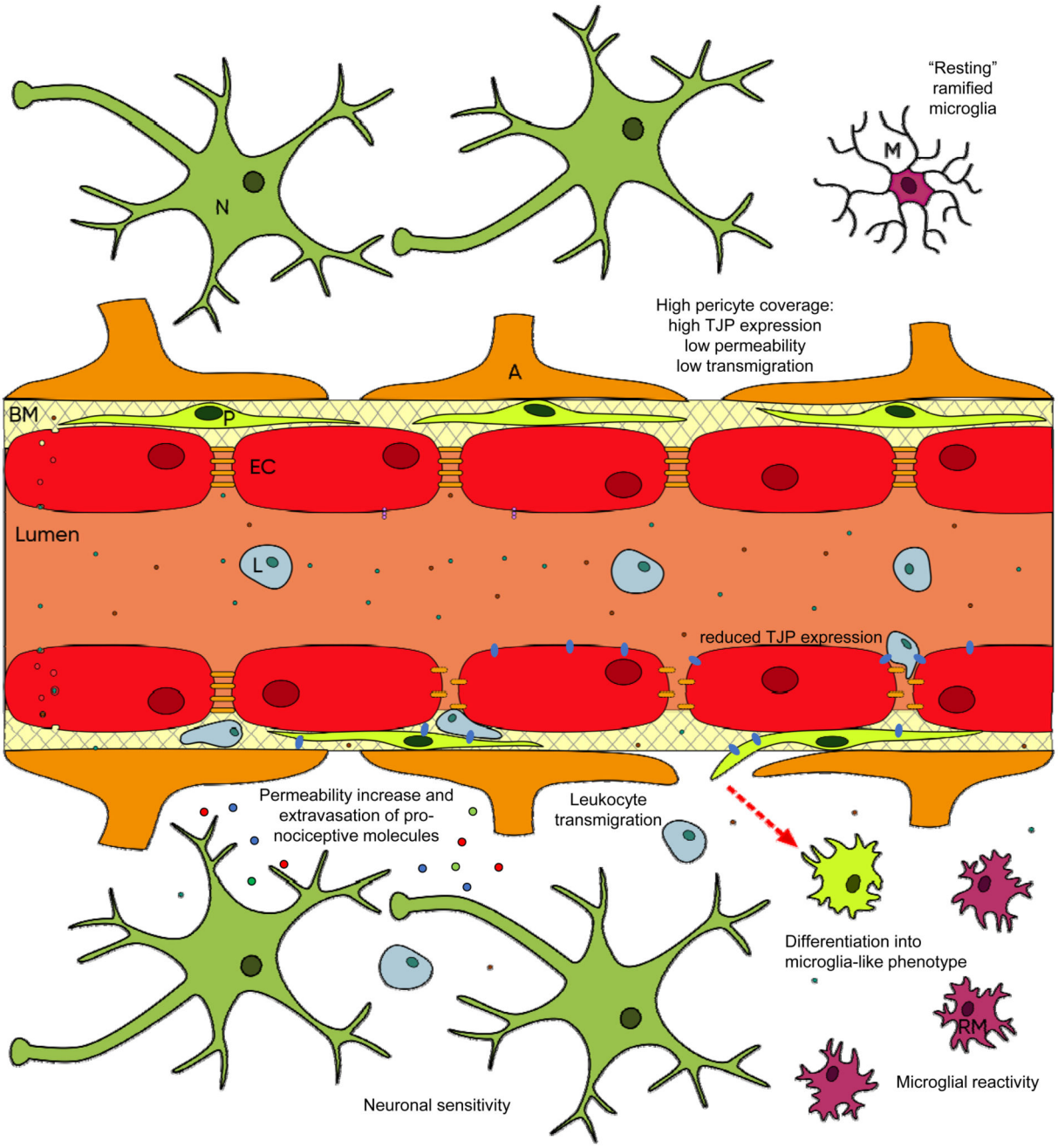

Figure 2.

Summary diagram of the roles pericytes play in CNS vascular biology that could contribute to neuronal sensitization and pain when dysregulated. High pericyte coverage induces high tight junction protein expression maintain low vessel permeability. A loss in pericyte coverage associated in pathological diseases results in decreased tight junction protein expression, consequent increased permeability and loss of vessel integrity. Extravasation of serum pro-nociceptive molecules, and pro-nociceptive and pro-inflammatory immune cell transmigration are likely to lead to neuronal sensitization and an increased pain state.

Pericytes are able to migrate into neuronal parenchyma and differentiate into a microglia-like phenotype, this mechanism may also contribute to an increased pain state.
Abbreviations: A- astrocyte; BM- basement membrane; EC- endothelial cell; L- leukocyte; M- microglia; P- pericyte; RM- reactive microglia.

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Table 1

Summary table of immune factors secreted by pericytes that are also implicated in nociception and pain states. Abbreviations: ICAM-1 intercellular adhesion molecule-1; VCAM-1 vascular adhesion molecule-1; CCL C-C-motif ligand; CXCL C-X-C motif ligand. IL interleukin; IFNγ interferon-γ; TNFα tumour necrosis factor-α; G-CSF granulocyte colony stimulating factor, GM-CSF granulocyte-macrophage colony stimulating factor; PDGF platelet-derived growth factor; VEGF-A vascular endothelial growth factor-a; iNOS inducible nitric oxide synthase; NOX-4 NADPH oxidase-4; MMP matrix metalloproteinase.

Immune family	Immune factor expressed by pericytes and implicated in nociception/pain states	Refs
Adhesion molecules	ICAM-1, VCAM-1	(27–30)
Chemokines	CCL2 (MCP-1), CCL4, CCL5, CCL11, CXCL1, CXCL10, CX3CL1	(31–35)
Cytokines	IL-1, IL1β, IL-2, IL-4, IL5, IL6, IL10, IL-17, IL-18, IL-33, IFNγ, TNFα, G-CSF, GM-CSF	(36–51)
Growth factor	PDGF, VEGF-A	(13, 52–54)
ROS/RNS	iNOS, NOX-4	(55–58)
Proteinases	MMP2, MMP9	(59, 60)