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Pericytes in the optic nerve head☆

Susannah Waxman [a], Deborah Villafranca-Baughman [b], Julie Phillippi [c], Tatjana C. Jakobs [d], Luis Alarcon-Martinez [e], Adriana Di Polo [b], Ian A. Sigal [a,f,*]

[a] Department of Ophthalmology, University of Pittsburgh, Pittsburgh PA, USA
[b] Department of Neuroscience, Université de Montréal, Montréal, QC, Canada
[c] Division of Cardiac Surgery, Department of Cardiothoracic Surgery, University of Pittsburgh, Montréal, QC, Canada
[d] Department of Ophthalmology, Massachusetts Eye and Ear Infirmary/Schepens Eye Research Institute, Harvard Medical School, Boston, MA, USA
[e] Centre for Eye Research Australia, Department of Ophthalmology, The University of Melbourne, Melbourne, Victoria, Australia
[f] Department of Bioengineering, University of Pittsburgh, Pittsburgh PA, USA

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ABSTRACT

Pericytes are a unique population of contractile mural cells and are an essential part of the microvasculature. In the retina and brain, pericytes play crucial roles in regulating blood flow, maintaining the blood-brain barrier, signaling with neighboring cells, and depositing extracellular matrix. Pericyte dysfunction is an early process in a variety of neurodegenerative conditions. However, remarkably little is known about pericytes at an early site of neurodegeneration in glaucoma, the optic nerve head (ONH). This work summarizes the current understanding of pericyte contributions to ONH physiology, identifies potential roles in glaucomatous pathophysiology, and uncovers open questions at the intersection of these areas. We surveyed the literature to identify the roles of ONH pericytes in the context of health and glaucoma. Additionally, we probed for the presence of pericytes along microvasculature in mouse, nonhuman primate, and human donor ONH tissues. We identified an association between factors influencing ONH dysfunction in glaucoma and factors influencing pericyte dysfunction in other neurodegenerative conditions. Pericytes exist in the mouse, nonhuman primate, and human ONH, implicating their capacity for local function. ONH pericytes represent a promising but underexplored target for treating microvascular impairment in glaucoma. Investigating the contribution of pericytes in both healthy and disease states can help inform mechanisms of dysfunction in glaucomatous pathology, paving the way for the development of novel therapeutic strategies.

1. Introduction

Pericytes comprise a unique population of mural cells and an essential part of microvasculature. Pericytes have a variety of key functions, including regulating blood flow through modulating capillary diameter (Kisler et al., 2017; Mishra et al., 2016; Peppiatt et al., 2006), signaling with neighboring cells, maintaining the blood-brain barrier (BBB) (Armulik et al., 2010; Dohgu et al., 2005), waste clearance (Dieriks et al., 2022; Kirabali et al., 2019; Ma et al., 2018; Munk et al., 2019; Stevenson et al., 2022), mechanosensing (Hariharan et al., 2020), and depositing extracellular matrix (ECM) (Dias et al., 2021; Schrimpf and Duffield, 2011). First described in the 1870s (Rouget, 1873; Stricker and Arnold, 1871) and latent for decades in the literature, the study of pericytes has recently gained significant momentum.

In the central nervous system (CNS), pericyte dysfunction has been demonstrated as an early process in several conditions associated with neurodegeneration, including Alzheimer's disease (Nortley et al., 2019; Sagare et al., 2013; Salmina et al., 2019), amyotrophic lateral sclerosis (Coatti et al., 2017; Yamadera et al., 2015), diabetic retinopathy (Durham et al., 2015; Hammes et al., 2002), and ischemia, such as in stroke (Cai et al., 2017; Hall et al., 2014; Yemisci et al., 2009). While aspects of pericyte distribution, blood flow regulation, and ECM deposition have been well-documented in the brain (Armulik et al., 2010; Hall et al., 2014; Kisler et al., 2017; Peppiatt et al., 2006; Sagare et al., 2013) and retina (Alarcon-Martinez et al., 2018; Barbosa et al., 2022; Hammes et al., 2002; Inman et al., 2005; Sakagami et al., 1999; Schallek

☆ 1 ONH pericytes.

* Corresponding author. Department of Ophthalmology, University of Pittsburgh, Pittsburgh PA, USA.
E-mail address: ian@OcularBiomechanics.com (I.A. Sigal).
URL: http://www.OcularBiomechanics.org (I.A. Sigal).

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et al., 2013), this cannot be said of an important region connecting these two areas, the optic nerve head (ONH, Fig. 1). The ONH is the site at which all ganglion cells of the retina converge to exit the posterior pole of the eye, forming the optic nerve (J. Salazar et al., 2019). The optic nerve connects to the brain, allowing for relay of action potentials and processing of visual signals (Laha et al., 2017; Prasad and Galetta, 2011). The ONH houses delicate neural tissue supported by a porous network of ECM and a dense plexus of microvasculature, requiring precise regulation to maintain homeostasis (J. Salazar et al., 2019; Prada et al., 2016).

Mechanical distortion of the ONH caused by ocular hypertension is a risk factor for glaucoma (Downs and Girkin, 2017; Tham et al., 2014), a leading cause of irreversible blindness. However, glaucomatous optic neuropathy can take place without ocular hypertension. Both in ocular hypertensive and normotensive glaucoma, vascular changes at the ONH are observable. These changes include impaired regulation of blood flow (Plange et al., 2003; Riva et al., 2004), altered BBB function (Arend et al., 2005), and shifts in levels of vasoactive compounds, such as increased endothelin-1 and decreased nitric oxide (Aliancy et al., 2017; Doganay et al., 2008; Good and Kahook, 2010; Li et al., 2016; Lommatzsch et al., 2022). Importantly, these changes are often detectable even in the early stages of the progressive disease. In addition to vascular dysfunction, pathological ECM remodeling (Crawford Downs et al., 2011; Hernandez and Pena, 1997) contributes to progressive retinal ganglion cell death and subsequent loss of vision. A correlation between pericyte function and glaucomatous changes, explored in detail in the following sections, suggests a potential for ONH pericytes in contributing to glaucoma pathogenesis.

This review focuses on the emerging knowledge of pericytes within the ONH. By examining direct evidence and drawing on insights from pericyte physiology in other CNS areas, we summarize the current understanding of pericyte contributions to ONH physiology. Investigating these contributions in both healthy and disease states can help inform mechanisms of dysfunction in neurodegenerative pathology, paving the way for the development of novel therapeutic strategies. Pericytes represent a promising but underexplored target cell population for treating diseases involving microvascular impairment, including glaucoma.

2. Pericyte localization and morphology

Pericytes are embedded within the basement membrane along the external wall of capillaries, in close proximity to vascular endothelial cells. The presence of pericytes has specifically been demonstrated in skeletal muscle, lung, liver, kidney, heart, adipose tissue, and the CNS (Hall et al., 2014; Hung et al., 2013; Lee and Chintalgattu, 2019; Moyle et al., 2019; Shaw et al., 2018; Wang et al., 2019; Zhang et al., 2016). Limited research exists regarding pericytes of the peripheral nervous system in contrast with the CNS. Pericyte morphology is heterogeneous and exists along a spectrum, with pericytes having ensheathing, mesh-like, or thin strand-like processes (Gonzales et al., 2020; Grant et al., 2019; Hartmann et al., 2015a; Smyth et al., 2018) (Fig. 2). Some works categorize pericytes into type 1 and type 2 groups, which are associated with health and disease states, respectively (Bohannon et al., 2021, 2024, 2025). Clear and widely accepted morphological criteria are not available to distinguish among these groups in the CNS. Although pericyte morphology varies, some features are conserved. Each pericyte has a prominent, rounded soma and nucleus, which is distinct from the elongated and flattened soma and nucleus of adjacent vascular endothelial cells. Multiple, slender, cytoplasmic processes can ensheathe the underlying capillary and contact other nearby cells

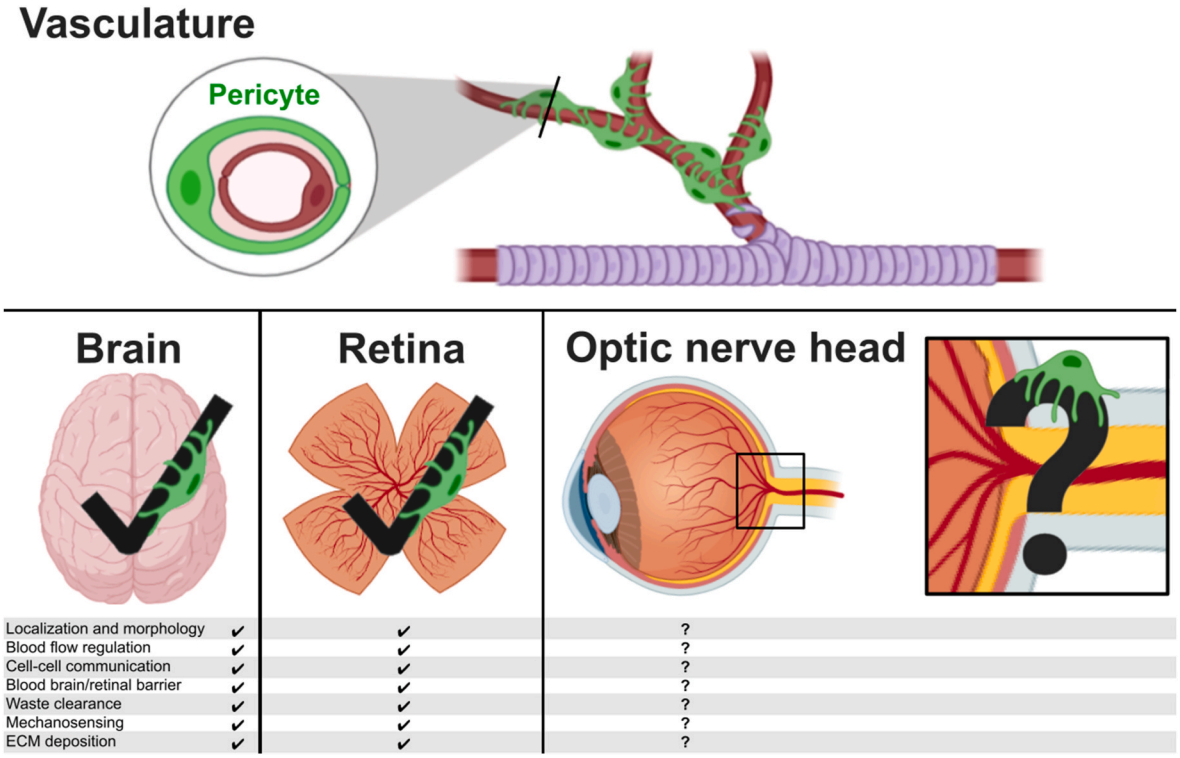

Fig. 1. Knowledge gap: the role of pericytes in health and disease of the ONH.
Pericytes exist along the external wall of capillaries, embedded within basement membranes (Fig. 1, top). They are known to play important physiological roles in the brain (Fig. 1, bottom left) and retina (bottom middle) and contribute to disease pathogenesis in prevalent neurodegenerative conditions such as Alzheimer's disease and diabetic retinopathy. However, the role of pericytes is not well documented in a critical region between the brain and retina, the ONH (Fig. 1, bottom right). Pericyte factors, (localization and morphology, blow flow regulation, cell-cell communication, blood-brain/blood-retinal barrier, waste clearance, mechanosensing, and ECM deposition) which are at least partially understood as a result of experimental data (✔) and factors which are not well understood (?) are discussed as they relate to the brain, retina, and ONH in the following sections. Created in part through BioRender.

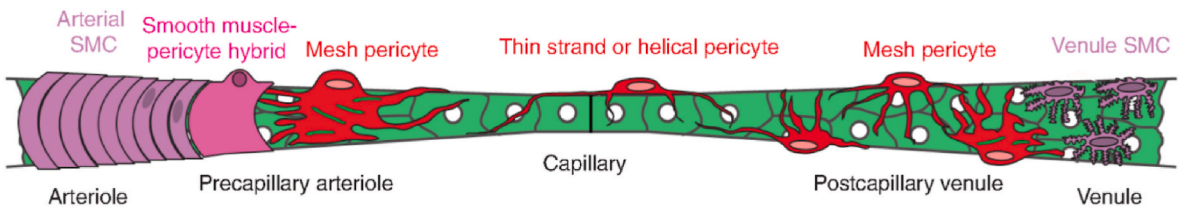

Fig. 2. Representative pericyte localization and morphology.
Schematic showing the continuum of mural cell types along the cerebral vasculature. Smooth muscle cells form concentric rings on arterioles. Hybrid smooth muscle-pericyte cells reside on precapillary arterioles and interlock with mesh pericytes at the arteriole–capillary interface, which occurs as penetrating arterioles ramify into the capillary bed. Pericytes in capillary beds typically exhibit long processes that traverse the microvasculature in single strands or pairs that twist in a helical fashion. Mesh pericytes become more prevalent again as capillaries turn into postcapillary venules. Stellate-shaped smooth muscle cells cover the walls of parenchymal venules. SMC: smooth muscle cell. Figure reproduced from (Hartmann et al., 2015a) with copyright permission.

(Alarcon-Martinez et al., 2021; Attwell et al., 2016; Grant et al., 2019; Hartmann et al., 2015a). Individual processes range from 2 to 130 μm in length, covering an average total distance of 250 μm per cell (Berthiaume et al., 2018).

Differences in pericyte localization and morphology relate to differences in their function (Alarcon-Martinez et al., 2021; Gonzales et al., 2020). For example, pericytes at microvascular branch points enable blood flow modulation across multiple vascular segments (Gonzales et al., 2020; Grubb et al., 2020). Pericytes at branch points and most proximal to arterioles tend to have ensheathing or mesh-like morphologies (Gonzales et al., 2020; Hartmann et al., 2015b). Pericytes along more distal capillaries and capillary segments without branches have more thin-strand morphologies, with less processes enwrapping underlying vasculature (Alarcon-Martinez et al., 2018; Gonzales et al., 2020; Hartmann et al., 2015b). Ensheathing and mesh pericytes generally express higher levels of alpha smooth muscle actin (**α**-SMA) than their thin-strand counterparts (Alarcon-Martinez et al., 2018,2021; Hartmann et al., 2015b), potentially indicating greater contractile capacity.

Notably, the density of pericyte coverage is positively correlated with endothelial barrier selectivity. In skeletal muscle, pericyte density is relatively low, at approximately 1 pericyte for every 100 endothelial cells. This contrasts with organs exhibiting tighter microvascular control, such as the lung (1 pericyte for every 8 endothelial cells) and the kidney and heart (both with approximately 1 pericyte for every 2.5 endothelial cells, (Geevarghese and Herman, 2014; Zhang et al., 2020). The highly selective endothelial layer of brain capillaries houses the highest density of pericytes in the body, with as many as one pericyte for every vascular endothelial cell (Bell et al., 2010; Mathiisen et al., 2010).

3. Labeling and identification of pericytes

Determining the identity, localization, and morphology of pericytes poses several unique challenges. Importantly, no single marker is universally accepted for distinguishing pericytes from other cells. Depending on the origin of the tissue, markers may label other resident cell populations in addition to pericytes. Furthermore, lineage tracing studies show that pericytes are a heterogenous population with diverse developmental origins (Armulik et al., 2011). As such, one marker may label only a subset of pericytes that are present. Therefore, utilizing a combination of pericyte markers, absence of non-pericyte markers, and/or cellular localization information is necessary for robust pericyte research. For example, pericytes are negative for von Willebrand factor, a commonly used vascular endothelial cell marker, which can help distinguish pericytes from nearby vascular endothelial cells (Trost et al., 2016). In preparations where cellular localization and morphology are preserved, these features can help indicate cell identity. In these cases, pericyte markers are commonly used in conjunction with vascular labels such as lectins, von Willebrand factor, or CD31, to determine the presence or absence of perivascular localization. While each of the existing strategies for pericyte identification have their respective shortcomings, many have proven to be highly valuable research tools.

3.1. Immunolabeling

Existing knowledge of the unique pericyte proteome is helpful in determining cell identity. Commonly used immunomarkers of CNS pericytes include neural-glial antigen 2 (NG2) and platelet-derived growth factor receptor β (PDGFR-β.) Immunolabeling for these pericyte targets has been used extensively to investigate pericytes in mice (Dominguez et al., 2015; Ozerdem et al., 2001) and rats (Hughes and Chan-Ling, 2004; Nortley et al., 2019). Although these antibodies are less well-validated in tissues of other origins, some work has shown pericyte immunolabeling in human donor tissues (Errede et al., 2021; Smyth et al., 2018). A more extensive list of immunomarkers that have been used to identify pericytes is included in Table 1.

NG2, also known as chondroitin sulfate proteoglycan 4 (CSPG4), is a membrane-bound glycoprotein that has been used extensively as a CNS pericyte marker. Much of the literature supports the idea that NG2-positive cells with perivascular localization along capillaries are indeed pericytes. However, the use of this marker can be confounding in the brain and optic nerve due to the existence of NG2-positive glia, notably oligodendrocyte progenitor cells (Dimou and Gallo, 2015; Yazdankhah et al., 2021). Some conflicting evidence exists to support that NG2-positive glia, not pericytes, are responsible for pericyte-like functions such as angiogenesis and vascular stabilization. For example, Minocha et al. concluded that the majority of NG2-positive cells in an NG2 reporter mouse model were not in fact pericytes, but NG2-positive glia: positive for the oligodendrocyte marker, Olig2, and negative for the pericyte marker, PDGFR-*β* (Minocha et al., 2015). In addition to NG2 expression in retinal pericytes, NG2 expression has been observed in vascular smooth muscle cells of the retina and ONH(Schallek et al., 2013; Shang and Schallek, 2024). Further complicating the matter, other work suggests the existence of pericyte subpopulations that are NG2-negative. In mice, cells expressing the pericyte marker Nestin with and without NG2 expression were observed, as well as NG2-positive cells with and without glial fibriliary acidic protein (GFAP) expression (Guo et al., 2013). In the human ONH, NG2-positive cells are present and have previously been categorized as NG2 glia (J. Salazar et al., 2019). This underscores the need for the use of multiple pericyte markers used in tandem to reliably and reproducibly identify this diverse cell type. Despite these conflicts, strong support exists for the idea that NG2-positive pericytes (GFAP-negative) are a population distinct from NG2-positive glia (GFAP-positive) (Guo et al., 2013; Minocha et al., 2015).

PDGFR-*β* is another transmembrane protein commonly used as a pericyte marker (Craggs et al., 2015; Song et al., 2005; Zachrisson et al., 2011). However, PDGFR-*β* can be expressed by vascular smooth muscle cells and some fibroblast populations (Chasseigneaux et al., 2018; Hewitt et al., 2012; Pellinen et al., 2023). Depending on how pericytes are defined, inconsistencies exist regarding which cell types were included in or excluded from analyses. For example, some studies have considered PDGFR-*β*-positive α-SMA-positive cells as vascular smooth muscle due to their α-SMA expression (Chasseigneaux et al., 2018),

Table 1
Common immunomarkers for CNS pericytes, localization of their targets, and possible off-target marker specificity (i.e., non-pericytes).

Marker	Localization	Specificity	Species	References
Neural/glial antigen 2 (NG2)	Membrane-bound	NG2 glia/oligodendrocyte precursor cells	mouse, rat, non-human primate, human	(Karram et al., 2005; Ozerdem et al., 2001; Peppiatt et al., 2006; Smyth et al., 2018; Stanton et al., 2015)
Platelet derived growth factor beta (PDGFR-β)	Membrane-bound	Vascular smooth muscle, fibroblasts	mouse, rat, non-human primate, human	(Bohannon et al., 2020; Hall et al., 2014; Smyth et al., 2018; Zachrisson et al., 2011)
Aminopeptidase N (CD13)	Membrane-bound	Mast cells, macrophage progenitor cells, synaptic membranes	mouse, human	(Fernández-Klett et al., 2013; Hartmann et al., 2015a; Nikolakopoulou et al., 2017; Smyth et al., 2018)
Alpha smooth muscle actin (α-SMA)	Cytoskeleton	Vascular smooth muscle, fibroblasts	mouse, non-human primate, human	(Alarcon-Martinez et al., 2018, 2019; Bohannon et al., 2020; Smyth et al., 2018)
Cluster of Differentiation 146 (CD146)	Cell surface adhesion molecule, can be secreted	Vascular endothelium, lymphocytes	mouse, rat, human	(Billaud et al., 2017; J. Chen et al., 2017; Smyth et al., 2018; Wittig et al., 2013)
Desmin	Cytoskeleton	Vascular smooth muscle	mouse, rat, cat, human	(Chan-Ling et al., 2004; Eilken et al., 2017; Hughes and Chan-Ling, 2004; Smyth et al., 2018)
Neuroepithelial stem cell protein (Nestin)	Cytoskeleton	Neural stem cells	mouse, rat	(Kim et al., 2016; Lee et al., 2012)

while others may include these cells as pericytes (Alarcon-Martinez et al., 2018). Pericyte expression of α-SMA is discussed further in the *Pericyte Contractility* section. PDGFR-*β*-positive cells with capillary-ensheathing morphology have been identified in the ONH of human eyes (Tovar-Vidales et al., 2016). Other notable CNS pericyte markers include CD13, CD146, desmin, Nestin, and α-SMA (Table 1).

3.2. Transgenic labeling

Mouse models engineered to express fluorescent reporters driven by promoters of commonly used immunomarker targets have been invaluable for identifying pericytes. This approach offers several advantages: pericytes can be identified *in vivo,* without additional labeling treatments that might alter cell physiology, and the boundaries of entire pericytes can be visualized, unlike with immunofluorescent detection of proteins localized only to specific cellular compartments. Common promoters used for fluorescent protein expression in these models include those driving NG2 (Hartmann et al., 2015a; Hughes et al., 2013; Zhu et al., 2008), PDGFR-*β* (Berthiaume et al., 2018; Cuttler et al., 2011; Hartmann et al., 2015a, 2015c), or a combination of both (Jung et al., 2018). It should be noted that use of a single genetically-driven reporter, without additional indicators of identity, is insufficient to distinguish pericytes from other cell types. The limitation to small animals like mice is a drawback, as robust techniques are needed to investigate pericytes in animals with ONHs more similar to humans, such as pigs and non-human primates, as well as in human donor tissues. There are substantial anatomical differences between the mouse ONH and the ONH of larger mammals, including humans (Elkington et al., 1990; Gogola et al., 2018; Morrison et al., 1995; Sun et al., 2009; Waxman et al., 2022). These anatomical differences are likely to impact the physiology of resident cells in health and under glaucomatous stress. Gene transfer to pericytes (Brandt et al., 2019; Wang et al., 2012; Yao et al., 2014) may prove to be a valuable *in vivo* and/or *ex vivo* tool to investigate pericytes in large animal models or postmortem human donor tissues.

3.3. Other labeling and detection methods

Other notable pericyte markers exist outside the previously mentioned categories. NeuroTrace (Damisah et al., 2017) is a Nissl dye which, upon topical application or intravenous injection, has been shown to label a subpopulation of capillary pericytes in the live mouse brain. This method is not suitable for post-mortem use, such as in donor tissues. Fluorogold was shown to label CNS pericytes after intraperitoneal injection in rodents, with effective visualization after 3–24 h in circulation (Edwards et al., 2013). Single-cell RNA sequencing allows for investigating pericyte clusters based on gene expression (Bohannon et al., 2024), but is destructive to tissues. Transcriptomic analysis of the eye's posterior segment suggests a *LAMA2*-positive and *TRPC4*-positive population of mural cells within the human ONH, consistent with possible pericytes (Monavarfeshani et al., 2023). Emerging spatial transcriptomic approaches, such as the Visium, Xenium (10× Genomics), and CosMx (nanoString) platforms, provide spatially-resolved gene expression information in tissue sections and new opportunities to investigate pericytes, *in situ.* Overall, identifying and visualizing pericytes presents unique challenges. Given that no single labeling or detection method is sufficient to identify pericytes unambiguously, using a combination of multiple approaches is particularly important to increase confidence in findings. Developing methods with high specificity and broad applicability would greatly benefit the field of pericyte research.

4. Pericytes in the ONH

Until recently, the existence of pericytes in the ONH of any species had not been well-documented. Pericytes associated with ONH capillaries have been recently reported in mice (Alarcon-Martinez et al., 2022). Additionally, in our preliminary studies using NG2-DsRed mice perfused intravascularly with fluorescently-tagged lectin, pericytes and vasculature were visible throughout the ONH (Fig. 3A). Although NG2-positivity alone is not sufficient to determine pericyte identity, these NG2-positive cells had characteristic bulbous somas closely apposed to microvessels and microvascular ensheathing morphologies. These features are distinct from ramified glia that can also express NG2. DsRed was expressed in vascular smooth muscle along larger vessels as well as in pericytes with microvascular localization. In the non-human primate ONH, immunolabeling revealed PDGFR-β localization along microvasculature (Fig. 3B), indicating the presence of pericytes. Similarly in the human ONH, the pericyte marker **α**-SMA was found along vasculature less than 10 μm in diameter (Fig. 3C), indicating potentially contractile pericytes along capillaries of these tissues.

Electron microscopy has shown that pericytes in other regions of the central nervous system are closely attached to the endothelial cells, with a thin basement membrane between them (Alarcon-Martinez et al., 2021; Nahirney and Tremblay, 2021). This basement membrane is particularly apparent in Fig. 4A. Pericytes characteristically "hug" capillaries (Nahirney and Tremblay, 2021). Pericyte processes can span longitudinally along the capillary in some cases, but a characteristic feature are processes that encircle most of the capillary if the capillary is cut transversely. Transmission electron microscopy showed pericyte ultrastructure in the mouse and human ONH, with pericytes embedded in capillary basement membranes (Fig. 4A–B). From EM examination, pericytes in the ONH are not obviously different from pericytes in other regions of the central nervous system (Alarcon-Martinez et al., 2021;

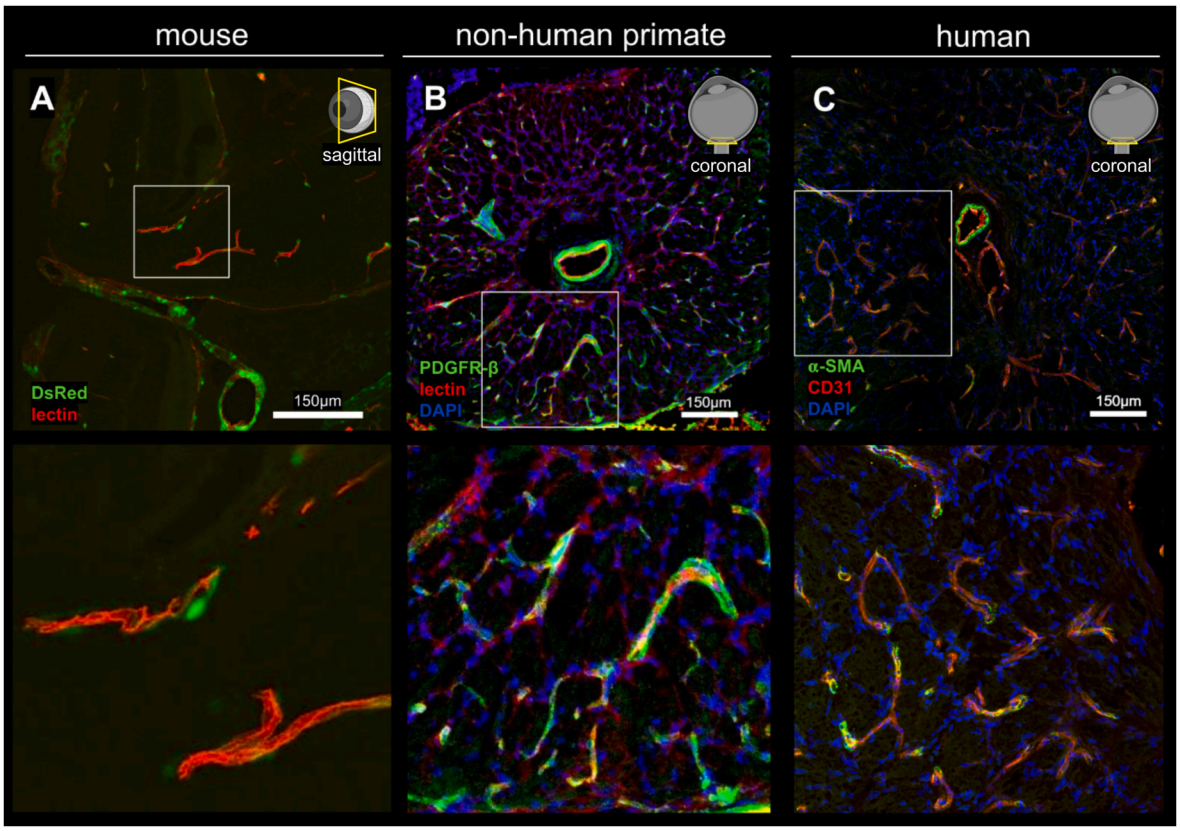

Fig. 3. Pericytes are present in the mouse, non-human primate, and human ONH.
In sagittal sections from eyes of NG2-DsRed mice perfused with fluorescently-tagged lectin, DsRed^{+} pericytes (green) were visible along microvasculature (red) in the ONH (A). In the non-human primate ONH (B), the pericyte marker PDGFR-β (green) was localized partly along lectin-labeled microvasculature (red), coronal view. In the human ONH (C), **α**-SMA (green) was found in part along CD31-positive microvasculature (red), coronal view. In B and C, nuclei are counterstained with DAPI (blue). Detail of the insets in the top row of is provided in the bottom row. The orientation of the sectioning plane for each sample is represented at the top right of A-C.

Nahirney and Tremblay, 2021). There are no characteristic features in their cytoplasm that would set them apart from other cells in EM. It is their shape and location that is characteristic. These findings document pericytes in the mouse, non-human primate, and human ONH. The presence of these pericytes suggests their potential for local function and dysfunction.

5. The role of pericytes in regulating blood flow

5.1. Neurovascular coupling

As a vital organ with higher metabolic demand than any other tissue in the body, the brain requires exquisite control of its vascular supply. Neurovascular coupling (NVC) ensures necessary blood flow to support tissue homeostasis as neural activity dynamically changes. With increased neural activity, an increase in blood flow must quickly follow. Neurons, astrocytes, microglia, vascular endothelial cells, and pericytes work in concert to meet the changing demands (Alarcon-Martinez et al., 2023; Wareham and Calkins, 2020). As one of the key cell types that comprise the neurovascular unit, pericytes contribute to NVC in the brain and retina (Alarcon-Martinez et al., 2020; Armulik et al., 2010; Hall et al., 2014; Hammes et al., 2002; Kisler et al., 2017; Peppiatt et al., 2006; Sagare et al., 2013). With abnormalities in ONH microvascular blood flow in glaucoma patients (Drance et al., 2001; Flammer et al., 2002; Harju and Vesti, 2001; Schwartz et al., 1977; Sugiyama et al., 2000; Zeitz et al., 2006), reaching a better understanding of the role pericytes play in NVC of this region would be highly valuable.

Similar to the brain, NVC is considered a form of blood flow regulation in the ONH (Falsini et al., 2002; Fondi et al., 2018; Prada et al., 2016; Riva et al., 1996, 2000, 2005). Non-invasive measurements of ONH blood flow can be made using laser Doppler flowmetry, laser speckle flowmetry, and optical coherence tomography angiography (Prada et al., 2016). Upon retinal exposure to a light-flicker stimulus, blood flow in the ONH is increased. Action potentials and the need for repolarization of retinal ganglion cell axon membranes are elevated with each flicker of light, causing regionally heightened metabolic demand. In the ONH of healthy anesthetized cats, nitric oxide levels increased in response to light-flicker stimuli and increase in blood flow was impaired upon inhibition of nitric oxide synthase (Buerk et al., 1996). Under healthy conditions, pericytes relax and dilate capillaries in response to nitric oxide, allowing for increased blood flow. For example, in the brain, a nitric oxide donor was shown to cause pericyte-mediated capillary dilation (Hall et al., 2014). Additionally, an inhibitor of nitric oxide production was shown to reduce constriction normally evoked by glutamate (Hall et al., 2014). Further studies are needed to elucidate the specifics of ONH NVC mechanisms under normal physiology.

NVC is impaired in glaucoma. Impaired nitric oxide signaling in glaucoma (Polak et al., 2007; Wareham et al., 2018) suggests its possible role in pericyte-mediated NVC dysfunction. In the retina, the vasculature's dilation response to light-flicker was diminished in eyes with glaucoma (Gugleta et al., 2012). In glaucomatous and/or hypertensive eyes of human subjects, light-flicker-induced NVC response was significantly reduced compared to healthy controls (Riva et al., 2004). In a chronic unilateral nonhuman primate model of glaucoma, vascular autoregulatory changes were observed at the ONH (Wang et al., 2014). To test dynamic intraocular pressure (IOP)-evoked autoregulatory

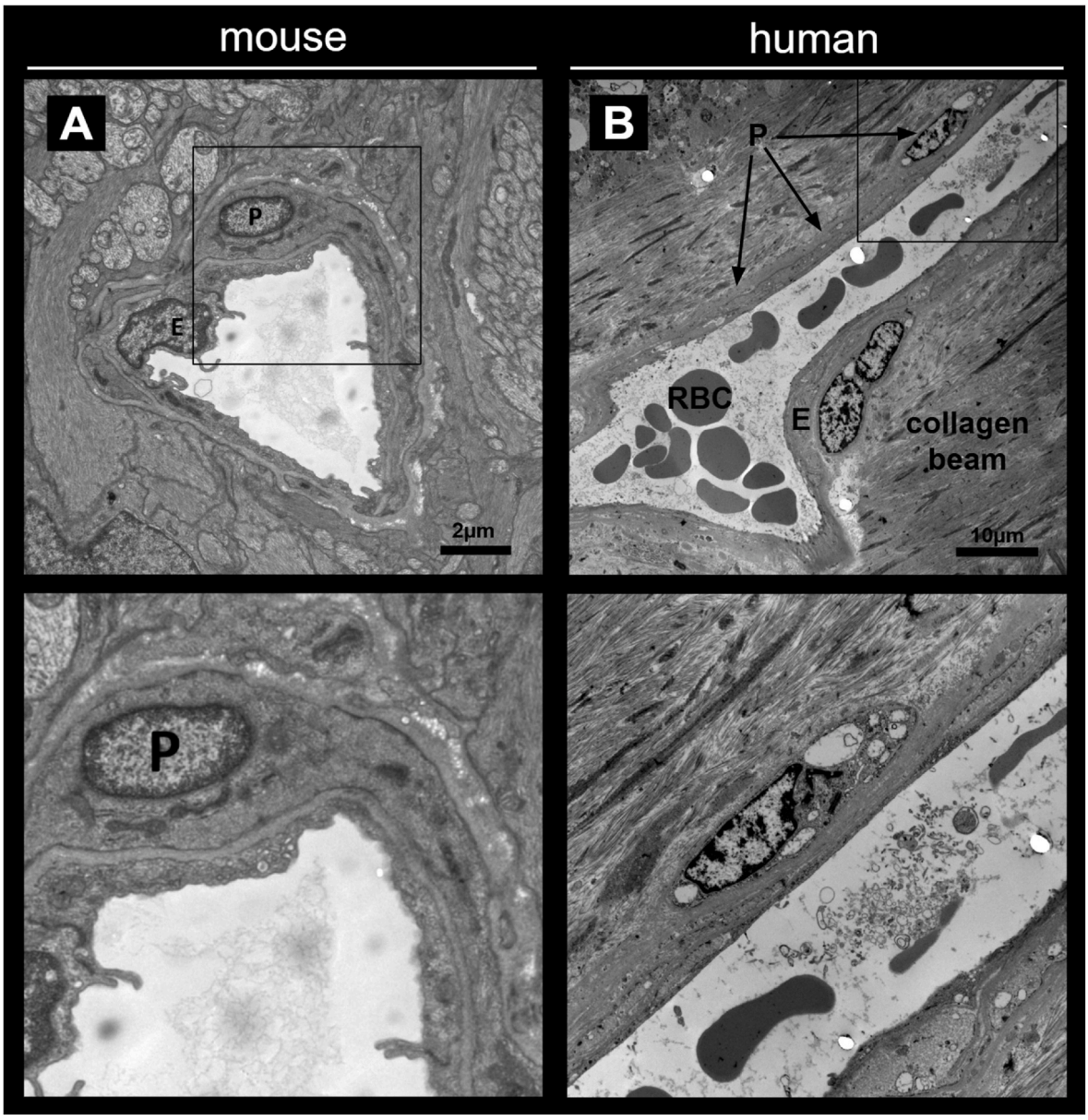

Fig. 4. ONH pericyte ultrastructure.
Transmission electron microscopy revealed ultrastructure of ONH pericytes in the mouse glial lamina (A) and human lamina cribrosa (B.) Pericytes were embedded within capillary basement membrane, in close proximity with endothelial cells. P: pericyte, E: endothelial cell, RBC: red blood cell. Detail of the insets in the top row of is provided in the bottom row.

response at the ONH, IOP was manometrically increased from 10 to 40 mmHg. Blood flow, blood flow response time, and the descending slope of the blood flow response changed in experimental glaucoma eyes. In contrast, no changes were observed in these features for fellow control eyes (Wang et al., 2014).

NVC is additionally impaired with aging and with systemic hypertension (Cai et al., 2023; Youwakim et al., 2023), both risk factors for glaucoma. For example, *in vivo* two-photon imaging revealed an age-dependent decrease in vascular responses to whisker pad stimulation in mice (Cai et al., 2023). The reduction in vascular responsiveness was particularly pronounced at precapillary sphincters, highlighting the aging-related role of these contractile regions in capillary blood flow regulation (Cai et al., 2023). Furthermore, systemic hypertension is associated with higher concentrations of circulating interleukin (IL)-17A (Madhur et al., 2010; Youwakim et al., 2023). Chronic administration of IL-17A in mice impairs NVC and neutralization of IL-17A or inhibition of its receptor prevents the NVC impairment (Youwakim et al., 2023). Overall, a better understanding of the mechanisms behind NVC impairment in glaucoma could be of great therapeutic benefit.

5.2. *pericyte contractility*

Pericyte contraction causes local changes in microvascular capacity, altering resistance to blood flow. In the brain and retina, pericytes can control capillary diameter (Alarcon-Martinez et al., 2019; Gonzales et al., 2020; Peppiatt et al., 2006) (Fig. 5), in turn affecting vascular supply to surrounding tissues. This mechanism directly contributes to the NVC response. Although smooth muscle cells can indirectly regulate blood flow at the level of capillaries (Longden et al., 2017), pericytes are the primary cells along CNS capillaries which can dynamically regulate blood flow through adjustment of contractile tone. The presence of contractile cells along the microvasculature in the ONH has significant implications for understanding local control of blood flow.

Similar to smooth muscle, a variety of studies have found that

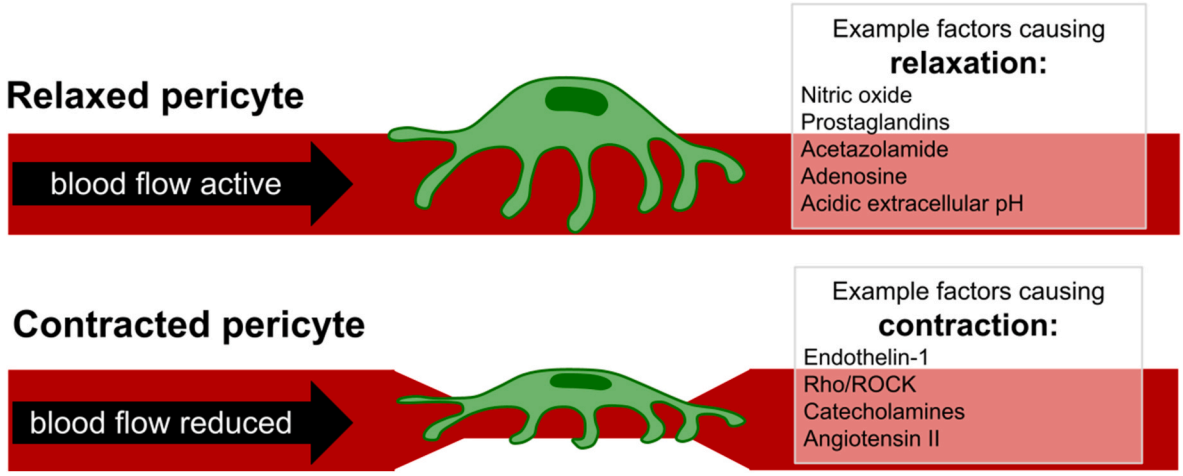

Fig. 5. Pericytes may regulate ONH blood flow.
In the brain and retina, pericytes (green) are the primary cells along CNS capillaries (red) which can dynamically regulate blood flow through adjustment of contractile tone. Relaxed pericytes allow for active blood flow through their resident capillaries. Contracted pericytes can reduce or halt local blood flow. In neurodegenerative conditions other than glaucoma, alterations in pericyte distribution, morphology, and contractile state have been observed as early and potentially causal disease processes. This could be true in glaucoma as well. The presence of ONH pericytes therefore has important functional implications in delivery of oxygen and nutrients to retinal ganglion cells in health and disease. Further details about factors causing relaxation or contraction of pericytes are included in Table 2.

pericytes are generally contractile in response to stimuli such as vasoactive compounds (Dehouck et al., 1997; Hall et al., 2014), mechanical stress (Dessalles et al., 2021), ischemia (Alarcon-Martinez et al., 2019; Yemisci et al., 2009), and electrical signaling (Peppiatt et al., 2006). However, other studies suggest that pericytes lack contractile ability or that only a subpopulation is contractile (Hill et al., 2015). These discrepancies may come down to differences in experimental methods. For example, the extent of visualization of the contractile marker α-SMA in retinal pericytes is dependent upon fixation technique (Alarcon-Martinez et al., 2018). Expression of contractile markers may be responsive to environmental stimuli, with pericytes possibly needing activation before becoming contractile. It is important to note that α-SMA is not the only indicator of contractile capacity; other contractile elements include F-acin (Kureli et al., 2020) and tropomyosin (Joyce et al., 1985).

Overall, there is strong evidence supporting the contractile capacity of CNSpericytes (Burdyga and Borysova, 2014; Hamilton et al., 2010; Peppiatt et al., 2006; Yemisci et al., 2009). Retinal ischemia induced capillary constrictions that colocalized with α-SMA-positive pericytes in mouse retina. These constrictions were reduced by the actin stabilizer phalloidin (Alarcon-Martinez et al., 2019), indicating that α-SMA mediates pericyte contraction under these circumstances (Alarcon-Martinez et al., 2019). Additionally, an L-type calcium channel antagonist decreased this contractile response, indicating that contractions are calcium-mediated (Alarcon-Martinez et al., 2019), in line with other studies (Alarcon-Martinez et al., 2019; Borysova et al., 2013; Burdyga and Borysova, 2014; Kawamura et al., 2002). Pericytes contract in response to factors such as increased cytosolic calcium concentration (Kamouchi et al., 2004; Khennouf et al., 2018), endothelin-1 (Kawamura et al., 2002; Neuhaus et al., 2017; Schönfelder et al., 1998), angiotensin II(Kawamura et al., 2004), and noradrenaline (Peppiatt et al., 2006). Relaxation of pericytes and dilation of microvasculature have been caused by factors including nitric oxide (Hall et al., 2014), adenosine (Gaudin et al., 2014), and decreased extracellular pH (Reber et al., 2003). Agents causing pericyte contraction often correspond with ONH damage while agents causing pericyte relaxation often correspond with an ONH protective effect. Common glaucoma pharmacologic treatments such as prostanoids, Rho kinase inhibitors, ACE inhibitors, alpha agonists, carbonic anhydrase inhibitors, and glucocorticoids affect pericyte contraction and relaxation. We observed α-SMA expression in ONH pericytes, suggesting pericyte contractile capacity in this region. Table 2101375 details agents known to affect both ONH pathology and pericyte tone. The wealth of stimuli affecting pericyte contractility allows for a highly dynamic, multi-factor system through which microvascular blood flow can be influenced.

6. Pericyte cell-cell communication

CNS pericytes exist as part of an interconnected neurovascular unit, communicating with neighboring pericytes and other cell types (Fig. 6) to orchestrate systems-level functions. In the liver, pericytes are known as hepatic stellate cells, which are often interconnected with other stellate cells, forming a functional unit referred to as the "stellon" (Wake, 2006). Recently, CNS research has similarly begun to discuss the pericyte "connectome" (Kovacs-Oller et al., 2020). Interconnected pericytes can signal to each other through intercellular gap junctions (Kovacs-Oller et al., 2020) and additionally, through tunneling nanotubes (Alarcon-Martinez et al., 2020, 2022). In the ONH, understanding the extent and redundancy of these functional connectivity units could have important implications for signaling and intercellular transport. CNS pericytes are uniquely positioned to act as intermediaries in communication between neighboring vascular endothelial cells, astrocytes, and neurons (Alarcon-Martinez et al., 2023; Wareham and Calkins, 2020).

Contacts between pericytes and vascular endothelial cells can occur through various junction types. Gap junctions connect the cytoplasm of these cells, enabling the transport of small molecules and electrical impulses (Cuevas et al., 1984; Kovacs-Oller et al., 2020). Adherens junctions couple the cytoskeletons of these cells, allowing for mechanical forces experienced by one cell to be shared or interpreted by the other (Dessalles et al., 2021; Geevarghese and Herman, 2014). Peg-and-socket junctions involve pericyte processes wedging into indentations of the vascular endothelium (Ornelas et al., 2021). The formation of tight junctions between microvascular endothelial cells depends on pericytes (Daneman et al., 2010; Jo et al., 2013; Wang et al., 2007). Additionally, paracrine interactions enable the essential role of pericytes in angiogenesis (Eilken et al., 2017; Kang et al., 2019; Stapor et al., 2014). Through communication with vascular endothelial cells, pericytes are recruited to vascular sprouts and are key in vascular assembly. In both the brain and retina, pericyte signaling with vascular

Table 2
Factors associated with ONH pathology/therapeutics which cause contraction/relaxation of CNS pericytes.

Factor	Effect in pericytes	Species	Role in ONH pathology/ therapeutics	References
Nitric oxide	Relaxation	mouse, rat, cow,	Frequently lower NO and impaired NOS in glaucoma, NO-donors Reduce IOP, neuroprotective	(Aliancy et al., 2017; Haefliger et al., 1994; Hall et al., 2014; Kovacs-Oller et al., 2020; Steele et al., 2009)
Prostaglandins	Relaxation	cow	Reduce IOP, neuroprotective in ONH	(Dodge et al., 1991; Hall et al., 2014; Ishida et al., 2006)
Acetazolamide	Relaxation	rat	Relaxed retinal pericytes, used as a glaucoma therapeutic	Reber et al. (2003)
Adenosine	Relaxation	mouse	Increases ONH blood flow, neuroprotective,	(Hariharan et al., 2022; Zhong et al., 2013)
Acidic extracellular pH	Relaxation	rat	Vitreous pH decrease found in acute glaucoma models	(Lu et al., 2001; Reber et al., 2003)
Endothelin-1	Contraction	mouse, cow	Endothelin-1 elevated in glaucoma, administration to the ONH causes neuropathy, antagonists lowered IOP and increased blood flow	(Dehouck et al., 1997; Good and Kahook, 2010; Nortley et al., 2019; Rosenthal and Fromm, 2011)
Rho/ROCK	Contraction	cow	ROCK inhibitors commonly therapeutic glaucoma	Kutcher et al. (2007)
Catecholamines	Contraction	mouse	Reduced blood flow in ONH	(Kelley et al., 1988; Peppiatt et al., 2006; Ubuka et al., 2014)
Angiotensin II	Contraction	rat, cow	Blockade of angiotensin II receptor is neuroprotective in glaucoma, receptor mutations associated with increased risk for glaucoma	(Matsugi et al., 1997; Yang et al., 2009)
Glucocorticoids	Apoptosis, inability to modulate	cow	Elevated IOP, can cause/exacerbate glaucoma	(Aliancy et al., 2017; Haefliger et al., 1994; Steele et al., 2009)
High glucose	Apoptosis, inability to modulate	mouse, cow, human	Diabetes is correlated with risk of glaucoma	(Podestà et al., 2000; Price et al., 2017)

endothelial cells plays a key role in BRB/BBB regulation through vitronectin-integrin interaction (Ayloo et al., 2022). The effects of pericyte-endothelial cell communication based on each of these avenues are vast, as evidenced by the involvement of pericytes in the many physiologic roles of microvascular endothelial cells.

As astrocytes interface with neurons throughout the CNS, pericyte communication with astrocytes serves as a crucial intermediate between blood vessels and neurons. The evidence for pericyte-astrocyte communication is largely indirect and incompletely understood. Astrocytes have been found to induce pericytes to synthesize vascular basement membrane proteins, playing an important role in maintenance of the BBB (Bonkowski et al., 2011). However, the exact mechanism by which this is accomplished is under-studied. Astrocyte secretion of APOE binds lipoprotein receptors of pericytes, leading to a proinflammatory cascade and contributing to BBB breakdown (Sweeney et al., 2016). Pericyte-mediated capillary dilation is regulated in part by calcium-dependent astrocyte signaling (Mishra et al., 2016). Despite the recognized importance of pericyte-astrocyte communication, there is still much to be learned in this space.

7. Pericyte involvement in the blood-brain and blood-retinal barriers

The high metabolic demand of the retina (Campbell and Humphries, 2012; Wolfrum et al., 2003) underscores the need for tightly regulated local vascular control. This control is mediated in part by the blood-retinal barrier (BRB), a functional interface between the bloodstream and the surrounding neural environment. Tight junctions between vascular endothelial cells in the retina allow for highly selective diffusion of molecules. BRB breakdown is a hallmark of several degenerative retinal diseases such as diabetic retinopathy (Eshaq et al., 2017), age-related macular degeneration (Cunha-Vaz et al., 2011), and cystoid macular edema (Campbell and Humphries, 2012). Pericytes are indispensable for the maturation of the BRB in mice (Park et al., 2017). Impaired pericyte recruitment disrupts the BRB, similar to that seen in diabetic retinopathy (Enge et al., 2002). Pericyte depletion in mice predisposes them to vascular leakage upon VEGF-A treatment, enlarged retinal vessels, microaneurysms, and hypoxia (Enge et al., 2002). In retinas with less than 50 % normal pericyte coverage, retinopathy was prevalent (Enge et al., 2002).

Like in the retina, pericytes play a vital role in the formation and maintenance of the vascular barrier in other CNS tissues (Armulik et al., 2010). Recent RNA sequencing work has provided transcriptional evidence of heterogeneity in brain pericyte roles in BBB regulation. The type-1 pericyte population was associated with BBB homeostasis while the transcriptionally-distinct type-2 pericyte population was associated with BBB breakdown (Bohannon et al., 2024). Additionally, healthy type-1 pericytes can transition into pathology-associated type-2 pericytes (Bohannon et al., 2024). These findings indicate that pericyte roles in BBB regulation are not only heterogenous, but plastic.

The optic nerve exhibits continuous, non-fenestrated endothelium with tight junctions, consistent with tissues with a classical BBB. However, there is variable evidence to support the presence of a BBB in the prelamina and lamina cribrosa regions of the ONH. In the 60s and 70s, perfused tracers were shown to extravasate and accumulate in the prelamina and lamina cribrosa, but not in the retrolaminar region or optic nerve (Flage, 1977, 1975; Hofman et al., 2001a,b; Tso et al., 1975). Some authors concluded that tracers reached the laminar regions due to extravasation from the peripapillary choroid, which has relatively higher vascular permeability (Hofman et al., 2001). Immunolabeling work indicates the presence of a BBB within some but not all regions of the ONH (Olsson and Kristensson, 1973; Peyman and Apple, 1972). PAL-E, an antigen present only in permeable capillaries, was absent in brain capillaries but present in the prelamina, suggesting that this prelamina region lacks a typical BBB (Hofman et al., 2001). The lamina cribrosa and retrolamina demonstrated PAL-E expression similar to the brain (Grieshaber and Flammer, 2007; Hofman et al., 2001). It has not been clearly demonstrated if or how ONH pericytes are involved in the ONH BBB. However, all regions with a BBB known to date are populated by pericytes, and therefore, pericytes likely also play a role in ONH BBB regulation (Armulik et al., 2010). Importantly, BBB disruption has been

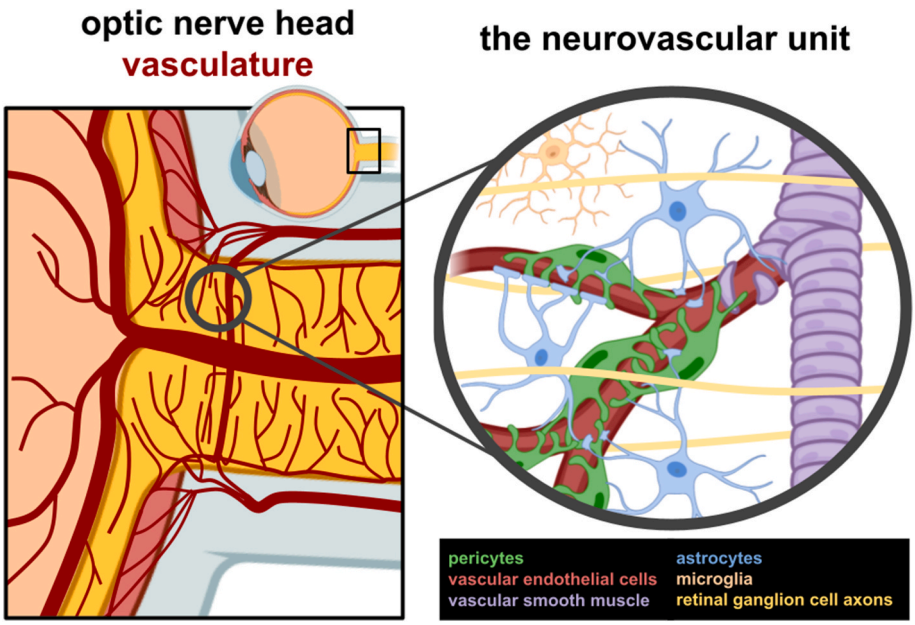

Fig. 6. The optic nerve head neurovascular unit: pericyte communication partners.
Pericytes are one cell type comprising the microvasculature within the ONH. ONH pericytes are in close proximity with other ONH neurovascular unit elements, including vascular endothelial cells, vascular smooth muscle cells, astrocytes, microglia, and retinal ganglion cell axons. The spatial relationships and molecular interactions of pericytes with surrounding neurovascular elements are likely to influence local neurovascular function in health and disease. Created in part through BioRender.

observed in the ONH of glaucoma patients (Arend et al., 2005; Grieshaber and Flammer, 2007); pericytes may play a role in this disruption.

8. Pericyte roles in waste clearance and glymphatics

Pericytes have been described as phagocytic cells, capable of actively taking up small molecules, circulating proteins, cell debris, and experimental loads such as polystyrene beads (Balabanov et al., 1996; Bergers and Song, 2005; Nortley et al., 2019; Thomas, 1999; Winkler et al., 2014). Pericytes can also express macrophage-like markers including CR3 complement receptor, CD4, and class I and II major histocompability complex molecules (Balabanov et al., 1996). As a result, pericyte dysfunction and/or degeneration can lead to accumulation of substances they normally process (Herland et al., 2016). This is particularly notable in the context of Alzheimer's disease, often associated with amyloid-β deposits (Murphy and LeVine, 2010). Amyloid-β accumulates within (Ma et al., 2018; Nortley et al., 2019) and can be cleared by (Kirabali et al., 2019; Ma et al., 2018) pericytes. Similarly, pericytes can uptake and degrade α-synuclein, aggregates of which are associated with Parkinson's disease (Dieriks et al., 2022; Stevenson et al., 2022). Age is a substantial risk factor for leading causes of neurodegeneration associated with waste aggregation (Hou et al., 2019; Jiang-Xie et al., 2024) and pericyte loss is associated with aging (Bennett et al., 2024). The decreased capacity of the remaining pericyte population to clear CNS waste products may play a role in age-related neurodegenerative conditions of the brain (Sengillo et al., 2013) and ONH (Guedes et al., 2011; Jammal et al., 2020).

In addition to the direct roles of pericytes in waste clearance, recent evidence supports the indirect and critical role of pericytes in waste clearance mediated by the glymphatic system (Iliff et al., 2012). The glymphatic system, first discovered in the rodent brain in 2012, is "the analog of the lymphatic system in the CNS" and plays important roles in local waste clearance (Iliff et al., 2012). Glymphatics were later similarly identified in the retina and optic nerve, where they can remove amyloid-β from the eye (Wang et al., 2020). These data suggest that impaired glymphatic waste clearance may be involved in the pathophysiology of neurodegenerative conditions, including Alzheimer's disease (Iliff et al., 2012), Parkinson's Disease (Dieriks et al., 2022; Stevenson et al., 2022), and glaucoma (Wang et al., 2020).

Interestingly, the ocular glymphatic system (Mathieu et al., 2017, 2018) relies on the water channel aquaporin-4 (AQP4), commonly expressed by astrocytes, for effective clearance (Wang et al., 2020). Astrocyte endfeet help to shape the perivascular channels of the glymphatic system and pericytes regulate astrocyte AQP4 endfeet polarization (Gundersen et al., 2014; Munk et al., 2019). Pericyte deficient mice had mislocated APQ4, impaired glymphatic development, and impaired clearance function (Munk et al., 2019). In the lamina cribrosa region of the ONH, an initial site of neural tissue injury in glaucoma, resident astrocytes are AQP4-negative (Kimball et al., 2022). Additionally, ocular glymphatic function was impaired as a result of elevated IOP (Mathieu et al., 2018) and intracranial pressure (Wang et al., 2020), indicating the importance of mechanics in glymphatic function. Future work is needed to understand the possible roles of ONH glymphatics and pericytes in ONH waste clearance.

9. Pericyte mechanosensing

Recent studies suggest that pericytes can respond directly to the mechanics of their environment and receive signals from other neighboring mechanosensitive cells. Pericytes are strategically located within the vasculature, embedded in the basement membrane, a highly collagenous structure. Given that collagen stiffness can significantly impact mechanosensing in various cell types (Wang et al., 2013), pericytes, in direct contact with the basement membrane, are well-positioned to detect changes in ECM stiffness and vascular tension. With ocular hypertension and ONH deformation playing substantial roles in glaucoma (Goldberg, 2003; Stamper, 2011; Sigal et al., 2005), mechanical stress from increased IOP could alter pericyte behavior and contribute to disease progression. This unique positioning and mechanosensitivity enable pericytes to sense mechanical signals that are crucial for maintaining vascular stability. Therefore, pericytes may be essential for regulating blood flow effectively, especially under pathological conditions like elevated IOP.

Several studies have pointed to the involvement of cellular

mechanosensing in glaucoma. Investigations have been conducted with focusing on trabecular meshwork cells, one of the key cell types regulating IOP, a primary risk factor for glaucoma progression (Asrani et al., 2024). Piezo1 is a mechanosensitive ion channel (Coste et al., 2010) expressed by the trabecular meshwork (Yarishkin et al., 2021; Zhu et al., 2021). Suppression of Piezo1 by GsMTx4 in mice reduced the facility of aqueous humor outflow through the meshwork (Zhu et al., 2021), leading to IOP elevation. Additionally, focus has been placed on ONH astrocytes, a key cell type involved in the neurodegenerative cascade characteristic of glaucoma. Piezo1 is additionally expressed by ONH astrocytes (Choi et al., 2015) and plays a functional role in their response to mechanical stimulation (Liu et al., 2021).

Pericytes in the brain have been shown to express Piezo1 (Hariharan et al., 2020). Additionally, in the brain and retina, vascular endothelial cell Piezo1 mediates mechanically-evoked calcium signaling (Harraz et al., 2022). Recent work further shows that endothelial Piezo1 acts as a mechano-feedback controller of brain blood flow, triggering calcium signals in capillaries and attenuating functional hyperemia by resetting vessels to baseline after neural activity (Lim et al., 2024). Pericyte-endothelial cell communication regulates blood flow regulation by influencing pericyte tone (Longden et al., 2021). Importantly, Piezo1-driven calcium signals are enriched specifically in capillary segments covered by contractile pericytes, suggesting a coordinated role between endothelial Piezo1 and pericytes in vascular regulation (Lim et al., 2024). Pericytes in the brain express several mechanosensitive channels in the transient receptor potential (TRP) ion channel family, including TRPC6, TRPP1, TRPV2, and TRPM3 (Hariharan et al., 2020). Interestingly, although TRPM3 expression has been observed in the ONH, it was not expressed by ONH astrocytes (Choi et al., 2015). It is possible but not yet known if TRPM3 is expressed by ONH pericytes.

Similarly, retinal pericytes express Piezo1 with Piezo1 mRNA and protein localizing to retinal capillaries and the ganglion cell layer. Piezo2 expression is also enriched in retinal ganglion cells and upregulated under elevated IOP conditions, suggesting a direct mechanosensory function in response to IOP changes (Harraz et al., 2022; Morozumi et al., 2020). Moreover, altered Piezo1 and Piezo2 vascular expression has been linked to diabetic neuropathy, with Piezo1 downregulated and Piezo2 upregulated in microvessels associated with neuropathic conditions (Garcia-Mesa et al., 2023), emphasizing the pathological relevance of vascular mechanosensing.

The heterogeneity of pericytes along the vascular tree plays a crucial role in ther mechanosensitivity. Ensheathing pericytes on pre-capillary arterioles exhibit high α-SMA expression and dense coverage, enabling strong contractile responses, whereas mid-capillary “mesh” and “thin-strand” pericytes display lower contractile protein levels and more limited coverage (Attwell et al., 2016; Grant et al., 2019). These location-dependent differences in contractile proteins suggest that mechanotransduction pathways and pericyte mechanosensitivity may vary depending on their position within the vasculature. However, capillary pericytes have also been shown to express α-SMA and to actively regulate blood flow, supporting a broader role for pericyte contractility beyond pre-capillary arterioles (Alarcon-Martinez et al., 2018, 2022). This variability adds complexity to understanding pericyte mechanosensitivity, emphasizing that their function may be tailored to specific vascular regions.

Overall, ONH pericytes are well-positioned as vascular mechanosensors: their embedding in the collagen-rich basement membrane and expression of mechanosensitive channels (Piezo1/Piezo2 and TRP family members) equip them to detect IOP-induced deformation or vessel stiffening, adjust contractility, regulate local blood flow, and influence ECM remodeling. However, direct investigations of these mechanosensitive processes in ONH pericytes and their role in glaucoma pathogenesis remains an important area for future research.

10. Pericyte contributions in ECM maintenance and fibrosis

Mechanical properties of the extracellular environment also critically influence pericyte behavior. Pericytes respond strongly to matrix stiffness: on relatively soft substrates they maintain their quiescent phenotype, whereas on pathologically stiff substrates they undergo a pericyte-to-fibroblast transition, acquiring migratory, invasive behavior (Feng et al., 2021). This matrix stiffness-induced transition is mediated by YAP activation, which drives loss of contractile markers and pericyte detachment from vessels, promoting fibrosis and vascular instability. Disease-associated vessel stiffening in the ONH likely alters pericyte mechanotransduction, though direct studies in ONH pericytes are lacking.

Pericytes play prominent roles in ECM maintenance and remodeling across various organs, including the liver, lung, kidney, muscle, and CNS (Dias et al., 2021; Hung et al., 2013; Moyle et al., 2019; Schrimpf and Duffield, 2011; Zhang et al., 2016). They are not only essential for building and maintaining a healthy ECM, but also contribute to aberrant ECM deposition in fibrotic diseases. Under pathological conditions, pericytes can differentiate into myofibroblasts, some of which migrate from their perivascular locations into surrounding tissue (Schrimpf and Duffield, 2011). This migration is associated with both production of fibrotic materials and a reduction of pericyte numbers along vasculature, leading to vascular instability.

In the brain, pericytes have been implicated in scar formation after ischemic insult (Fernández-Klett et al., 2013), traumatic brain injury, and after encephalomyelitis (Dias et al., 2021). In the spinal cord, a specific subset of pericytes is required for scar formation (Dias et al., 2018; Goritz et al., 2011). Some evidence suggests that pericytes in the retina and optic nerve may differentiate into myofibroblasts, influencing pathologic remodeling in these regions. In the retina, an increase in collagen IV deposition around microaneurysms correlated with increased local pericyte coverage (López-Luppo et al., 2017). This suggests a contributing role for pericytes in CNS fibrosis and vascular basement membrane remodeling. Pericyte immunolabeling with connective tissue growth factor (CTGF), a factor that can stimulate extracellular matrix formation and fibrosis, was increased in retinas of diabetic donors (Kuiper et al., 2004). In a PDGFRβ-P2A-CreER^{T2}-tdTomato mouse line, pericyte-derived cells were found to contribute to fibrotic scar formation in the optic nerve after optic nerve crush (Preishuber-Pflügl et al., 2023). The number of pericyte-derived cells within the lesion increased over time, with up to 90 % of PDGFRβ+ scar-forming cells derived from pericytes (Preishuber-Pflügl et al., 2023). This indicates a role of pericyte-derived cells in fibrotic scar formation following injury. Future work is needed to determine the fibrotic capacity of pericytes, specifically in the ONH of eyes with a collagenous lamina cribrosa, like in humans.

Abnormalities of the perivascular ECM have been observed in the ONH in disease contexts. In glaucoma, both human and mouse model studies have shown that capillary ECM sheaths in the prelaminar region are significantly thicker compared to those in healthy eyes (Zhu et al., 2018). Transmission electron microscopy images support these findings, showing perivascular cells linked to these changes (Hernandez et al., 1990; Tektas et al., 2010). In Susac’s syndrome, which can lead to progressive vision loss, thickened capillary walls adjacent to pericytes exist in the ONH (McLeod et al., 2011). Pericytes produce TGF-β during blood vessel maturation (Chen et al., 2017) and can produce higher levels in pathologic conditions (Rustenhoven et al., 2016). TGF-β is highly upregulated during glaucomatous ONH remodeling, and exogenous TGF-β treatment has been shown to increase ECM synthesis (Zode et al., 2011). In the advanced glaucomatous ONH, collagen density is generally higher than in healthy eyes (Belmares et al., 2018). Pericytes are known to synthesize and deposit collagen types I and IV, laminin, fibronectin, and vitronectin (Zhao and Chappell, 2019), all of which can be involved in scar formation. Moreover, pericytes can induce ECM production indirectly through interactions with endothelial cells

(Breitkreutz et al., 2004). Pathological remodeling and ECM deposition are hallmarks of the glaucomatous ONH. The specific role of pericytes in ECM remodeling of the ONH in disease remains underexplored.

Astrocytes in the ONH can become activated in response to insult (Qu and Jakobs, 2013), leading to glial scarring. Due to their similar perivascular locations and responses to stimuli, methods targeting astrocytes may also inadvertently affect pericytes. Methods to differentiate each cell type's contribution in ECM remodeling and fibrosis are limited. Regardless of whether a particular fibrotic component has been deposited by astrocytes, pericytes, or another cell type, pericytes are influenced by their surrounding microenvironment. *In vitro* studies indicate that resting pericyte tone (Islam et al., 2024) and pericyte traction forces (Iendaltseva et al., 2020) are influenced by substrate stiffness, potentially contributing to a pro-fibrotic feedback loop.

This influence of substrate stiffness has important implications for pericyte mechanosensing, both directly via pericytes and indirectly through their communication with nearby mechanosensitive cell types experiencing similar mechanical environments. Given the significant roles pericytes play in fibrosis of tissues outside the ONH, they should be considered as targets for investigation and therapy in ONH fibrosis as well.

11. Current and future pericyte-focused therapies

Over the past decade, pericytes have been increasingly recognized as potential drug targets in various pathologies. Due to their crucial role in angiogenesis, drugs targeting pericytes have primarily focused on tumor neovascularization (Chen et al., 2017) and disrupting tumor vasculature. In most tumor types, pericytes are present along microvasculature. Tumor blood vessels with dense pericyte coverage have shown resistance to vascular disrupting agents. Pericytes in malignant tumors often have a different expression profile to those of pericytes in the rest of the body, potentially enabling specific targeting of these pericytes for therapeutic purposes (Chen et al., 2017).

Pericyte-targeted therapies have been tested through the use of antibodies, gene therapy, small molecules, and peptides. Markers that are highly expressed in pericytes have been exploited for preferential targeting of tumor pericytes. Blockade of PDGFR-β led to regression of pericytes and a resulting increase in vascular permeability (Kang and Shin, 2016). Peptide-conjugated liposomes loaded with chemotherapeutics targeted to PDGFR-β-positive cells and have been shown to increase efficacy of anticancer drugs. In mice, chemotherapeutic-loaded nanoparticles decorated with TH10, a peptide with high affinity for NG2, resulted in selective internalization of the particles by NG2-expressing pericytes. This resulted in an inhibition of tumor angiogenesis (Guan et al., 2014). In separate studies, human serum albumin was conjugated to both CSRNLIDC, a peptide with high affinity for PDGFR-β, and the chemotherapeutic doxorubicin. Administration of these conjugates in mice resulted in drug accumulation in PDGFR-β-expressing pericytes, inhibition of angiogenesis, and reduced tumor volume (Prakash et al., 2010a, 2010b).

Pericytes are essential for regulating the BBB, demonstrating stem-cell-like regenerative properties. This makes them excellent targets for BBB repair. Delivery of exogenous pericytes into the CNS has been proposed as an avenue for regenerative therapies, potentially using autologous pericytes derived from patient adipose tissue (Zannettino et al., 2008). However, a lack of clinical standards for pericyte isolation complicates this approach. Differentiating patient-derived stem cells or induced pluripotent stem cells *in vitro* could help address these complications. Research suggests that seeding healthy and/or genetically modified pericytes may offer protective benefits (Courtney and Sutherland, 2020). However, like all stem-cell therapies, caution is advised due to the variable differentiation potential of pericytes, which could lead to ectopic tissue formation or tumorigenesis. A deeper understanding of pericyte behavior in both healthy and disease states of the ONH may support a precision medicine approach.

No existing therapies are known to target ONH pericytes specifically. However, as ONH BBB disruption has been observed in glaucoma patients (Arend et al., 2005), pericyte modulation may be capable of ONH BBB repair. Additionally, neurodegeneration in glaucoma is preceded by microvascular regression in the ONH (Drance et al., 2001; Flammer et al., 2002; Harju and Vesti, 2001; Lee et al., 2017; Schwartz et al., 1977; Sugiyama et al., 2000; Zeitz et al., 2006). Future therapies may be able to leverage the angiogenic capacity of pericytes to restore microvascular density lost in glaucoma. This restoration of microvascular density has the potential to restore healthy blood flow to the region and protect ONH tissues from the metabolic deficit that can cause irreversible neurodegeneration.

12. Conclusion

Despite their established importance in brain and retina health and disease, pericytes are poorly understood in a critical area connecting these two: the ONH. The ONH is a primary site for irreversible glaucomatous neuropathy, a leading cause of blindness worldwide. Pericytes regulate microvasculature in the CNS. Given the significant vascular aspect of glaucoma, understanding their distribution and function in the ONH can provide immense biomedical benefits. Currently, no therapies specifically target pericytes in the ONH. However, insights into pericyte distribution, regulation of blood flow, cell-cell communication, BBB maintenance, waste clearance, mechanosensing, and ECM remodeling have already spurred promising experimental strategies in the CNS to address dysfunction. Investigating the similarities and differences of ONH pericytes with pericytes of other CNS tissues could help identify which strategies may translate into effective treatments. Additionally, these investigations can inform innovative strategies to address diseases involving microvascular dysfunction, including glaucoma.

CRediT authorship contribution statement

Susannah Waxman: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Deborah Villafranca-Baughman:** Writing – review & editing. **Julie Phillippi:** Writing – review & editing. **Tatjana C. Jakobs:** Writing – review & editing, Resources. **Luis Alarcon-Martinez:** Writing – review & editing. **Adriana Di Polo:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Ian A. Sigal:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

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J. Phillippi: **None**.

I. A. Sigal: **None**

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Data availability

Data will be made available on request.

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