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Review

Pericytes in the disease spotlight

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Pericytes are known as the mural cells in small-caliber vessels that interact closely with the endothelium. Pericytes play a key role in vasculature formation and homeostasis, and when dysfunctional contribute to vasculature-related diseases such as diabetic retinopathy and neurodegenerative conditions. In addition, significant extravascular roles of pathological pericytes are being discovered with relevant implications for cancer and fibrosis. Pericyte research is challenged by the lack of consistent molecular markers and clear discrimination criteria versus other (mural) cells. However, advances in single-cell approaches are uncovering and clarifying mural cell identities, biological functions, and ontogeny across organs. We discuss the latest developments in pericyte pathobiology to inform future research directions and potential outcomes.

Highlights

Molecular and functional pericyte studies at single-cell resolution are providing new insights into long-standing questions about pericyte heterogeneity.

Pericytes are not identified by a single marker but instead by gene expression signatures that show substantial inter-organ differences.

Pericytes orchestrate and precede endothelial cell responses during angiogenesis.

Pericyte degeneration and dysfunction, that are triggered by the onset of some diseases, contribute to the progression of those diseases in both vascular and non-vascular contexts.

The number of diseases with pericyte dysfunction continues to expand, thereby anticipating a promising future for pericyte-focused therapy.

Multifaceted roles of mural cells in health and disease

Pericytes are classically defined as **mural cells** (see Glossary) that envelop the endothelium of small caliber blood vessels, the so-called capillaries. Pericytes are embedded within the same basement membrane as endothelial cells (ECs) and interact closely with them [1,2]. By contrast, vascular smooth muscle cells (vSMCs), the other mural cell type, cover large arteries and veins, and are physically separated from the endothelium by an intimal layer of extracellular matrix (ECM). Of note, lymphatic capillaries lack pericytes under physiological conditions, although collecting lymphatic vessels contain vSMCs [3].

A fundamental function of mural cells is to regulate the stabilization and function of blood vessels. It is therefore not surprising that pericyte loss and dysfunction were linked to several diseases including cancer and cerebrovascular diseases more than a decade ago [4,5]. However, pericyte-focused therapies have been poorly explored. Instead, most studies on vascular-directed therapeutic strategies have been on ECs – the central components that build blood vessels. Emerging data are, however, changing the perception of pericytes from mere supporting vascular cells that are recruited at the final stage of vessel formation to essential elements in the early phases of **angiogenesis** that anticipate and orchestrate EC behavior. In addition, recent research is revealing novel pathological roles for pericytes beyond their implications in the vasculature. Collectively, we believe that these data open exciting avenues for pericyte-focused therapeutic approaches and call for a broader understanding of these cells in disease progression.

We provide here a global overview of recent significant advances regarding our understanding of the role of pericytes in different pathobiological scenarios and discuss the field's current paradigms and controversies. First, we address new insights into the functions associated with pericytes during physiological vascular responses. Second, we discuss evidence supporting a role of pericytes in disease, including pericyte cell-autonomous implications beyond the vasculature. For comprehensive details on pericyte biology, function ontology, and specific signaling pathways, we refer the reader to [1,2,5]. Of importance, some of the emerging concepts in pericyte biology described in the following sections have only been studied in one specific tissue. To avoid confusion about the generalizability of pericyte properties, we frame each function by considering the relevant organ of study.

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Key concepts about pericytes in physiology

Pericytes: a particular subtype of mural cells

Pericytes exhibit significant inter- and intra-tissue molecular differences and exert tissue-specific functions [2]. Their molecular, morphological, and functional heterogeneity is inextricably linked to their diverse developmental origins, modes of vessel recruitment, and specific anatomical localization. For example, pericytes of the central nervous system (CNS) microvasculature are firmly and continuously invested around the endothelium to support vascular barrier properties, whereas liver pericytes, commonly referred to as hepatic stellate cells (HSCs), reside in the perisinusoidal space, are loosely and discontinuously associated to ECs, and hold a unique vitamin A storage capacity [2]. To meet tissue-specific demands, pericyte distribution and density are variable among organs and vascular beds, with the CNS microvasculature showing the greatest pericyte-to-EC abundance. From a molecular standpoint there is no single molecular marker that can exclusively identify pericytes (Box 1), albeit the emergence of single-cell techniques is shedding light on tissue-specific pericyte molecular markers and functions. For example, the first molecular atlas of vascular cell types in the brain of adult mice by single-cell RNA sequencing (scRNA-seq) revealed that mural cells follow a gradient of transitional phenotypes. This gradient occurs at the interface of precapillary arterioles, capillaries, and postcapillary venules, and does not follow a single continuum along the arteriovenous axis (Figure 1 and Box 1) [6]. Whether this gradient of transitional phenotypes is specifically restricted to the brain vasculature or is also present in other vascular beds remains to be determined. Indeed, pericytes exhibit many organotypic differences in the expression of molecular markers (Figure 2 illustrates three top-ranked pericyte markers with enriched expression per organ), of which the expression of transporters and components of the contractile machinery exhibit the greatest differences between organs [7]. Another intriguing observation is that pericytes exhibit more cross-organ heterogeneity than vSMCs [7,8]. Currently, the inter-tissue differences in the behavior of the two main mural cell types are not completely understood. However, this may be because pericytes exhibit a greater cell-intrinsic plasticity to adapt their molecular portfolio and function to tissue-specific demands, whereas vSMCs fulfill a more universal function across tissues. In contrast to the tissue-specific transcriptomic differences, the expression of transcription factors appears to be relatively conserved in mural cells across organs, thereby suggesting that mural cell subtypes are defined

Box 1. Unraveling the identity of pericytes

The identification of pericytes remains a challenging task. Despite ongoing efforts, there is no consensus regarding unambiguous criteria for pericyte identification. To date no single molecular marker can exclusively identify all pericytes or distinguish pericytes from other cell types, although scRNA-seq is now providing new opportunities to discern pericyte marker heterogeneity and tissue specificity [6,8,71,93]. The use of transgenic reporter mouse models has been instrumental to label, trace, and locate different mural cell populations *in vivo*. A combination of multiple reporter lines is often necessary to properly identify and discriminate pericytes from endothelial cells (ECs) and other perivascular cells [6–8]. Mural cells are highly plastic cells; phenotypic zonation of mouse brain mural cells has revealed that these cells do not follow a single continuum along the arteriovenous axis (see Figure 1A,B in main text) [6]. From a transcriptional point of view, there are two distinct continuums of mural cells: (i) capillary pericytes and venous smooth muscle cells (SMCs), where pericytes gradually transition to a venous SMC phenotype, and (ii) arterial SMCs which transition in an distinct pattern towards arteriole SMCs. The transcriptional resemblance between mouse brain pericytes and venular mural cells [6], as well as the lack of classic pericytes in several organs [7,8], have led to the hypothesis that capillary pericytes are transcriptionally and morphologically similar to venous SMCs in some tissues. Human brain mural cells recapitulate the mouse zonation pattern, although human pericytes are evenly distributed over capillaries and veins [50,94]. Unlike the anatomical separation of pericytes and venous SMCs in the mouse brain, subtypes of human pericytes are discerned by functionality marked by solute transport and extracellular matrix (ECM) organization [50]. Unfortunately, the ability of mouse markers to predict the presence of human pericytes remains limited, and only a select few retain adequate specificity. The use of zebrafish models may provide a better alternative to study conserved pericyte genes [95]. We believe that *RGS5*, *NDUFA4L2*, *KNCJ8*, *HIGD1B*, *ABCC9*, *NOTCH3*, and *PDGFRB* are currently the most organ and species conserved pericyte markers, although detailed intra-tissue characterization remains necessary when studying pericytes (see Figure 2 in main text).

Glossary

Angiogenesis: the formation of new blood vessels by expansion of pre-existing vessels.
Blood–brain barrier (BBB): a metabolic and physical barrier property of the brain vasculature which controls selective and hemodynamically responsive transport of molecules between the blood and the brain. It is composed of a specialized non-fenestrated endothelium that is sustained by tight intercellular junctions, in conjunction with the essential support of pericytes, astrocytes, microglia, and neurons.
CADASIL: abbreviation of cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy, a disease that occurs when the thickening of blood vessel walls blocks the flow of blood to the brain.
Capillary stalling: a pathological process by which stalled leukocytes or constriction of capillary pericytes blocks capillary blood flow.
Co-opted vessels: a non-angiogenic process through which tumor cells make use of pre-existing resident blood vessels to sustain tumor growth.
Mural cells: cells which surround the endothelium of blood and lymphatic vessels and support their function. They comprise a heterogeneous cell population with a variety of tissue-dependent phenotypes, and are largely grouped into pericytes and vascular smooth muscle cells (vSMCs).
Neurovascular coupling: the tight physiological coordination between neuronal activity and changes in local blood flow to match the oxygen and nutrient demands of active brain regions.
Pericrine signaling: pericyte-derived signals that act on neighboring cells.

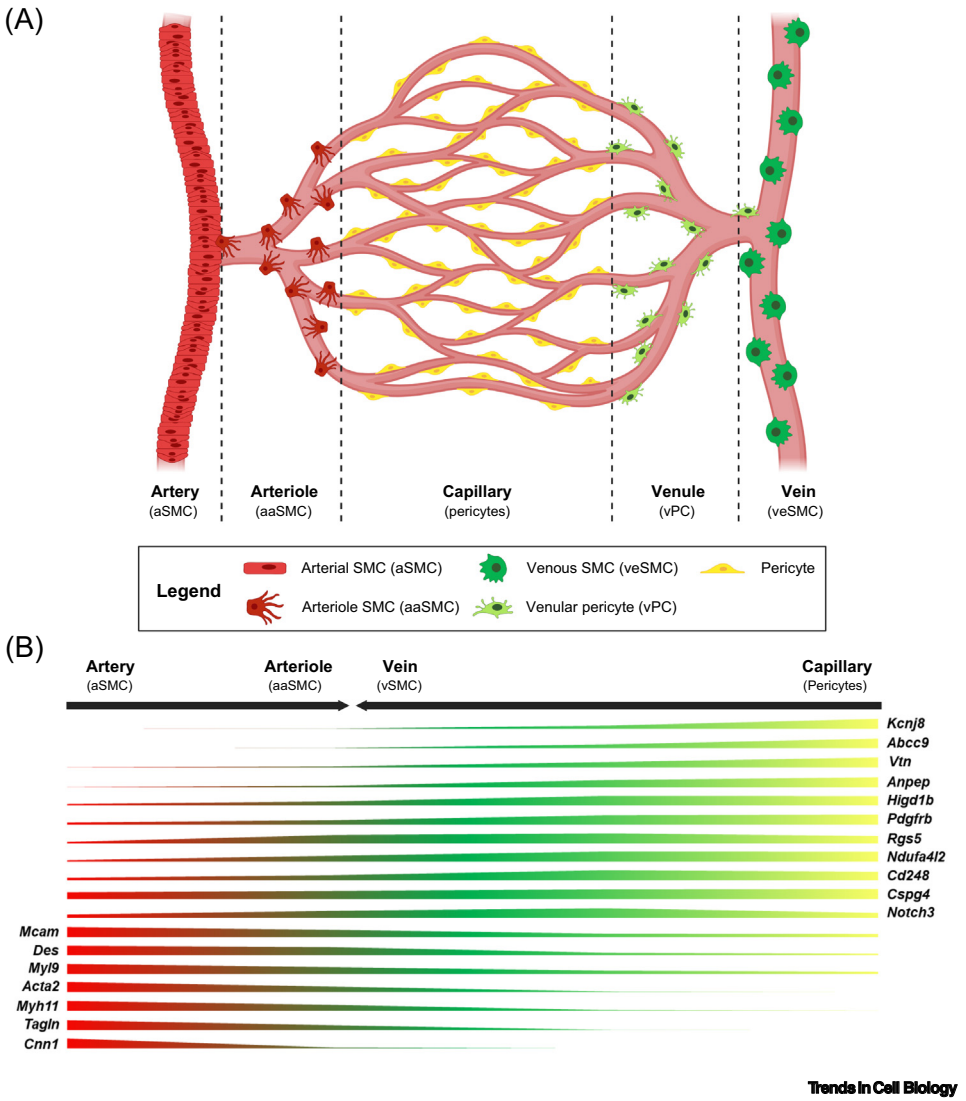

Figure 1. Schematic representation of mural cell zonation in the adult mouse brain. (A) Localization on the arteriovenous axis, and (B) transcriptional gene expression of common molecular markers associated with mural cells. Brain mural cells are classified into distinct phenotypic gradients (indicated by the black arrows): arterial smooth muscle cells (aSMCs) with arteriole SMCs (aaSMCs), and capillary pericytes with venous SMCs (veSMCs). Mural cells located on venules are transcriptionally similar to pericytes and are hence referred to as venular pericytes (vPCs). Compared to pericytes and veSMCs, aSMCs and aaSMCs express high amounts of contractility genes such as *Tagln*, *Acta2*, *Myh11*, and *Cnn1* (in red). *Kcnj8*, *Abcc9*, and *Vtn* (in yellow) are examples of markers most specific for pericytes, although they are also expressed by veSMCs (in green). Of note, canonical markers *Anpep* and *Cd248* are specific for brain pericytes but lose their predictive value in most other tissues, indicative of organotypic specialization. The markers *Pdgfrb*, *Cspg4*, *Rgs5*, and *Notch3* demonstrate broad expression in all mural cells and appear to be most conserved.

by epigenetic mechanisms [7]. Accordingly, DNA hypermethylation was recently found to control alpha smooth muscle actin (αSMA) expression in renal mural cells after ischemia [9]. This indicates that methods such as assay for transposase-accessible chromatin sequencing (ATAC-seq) will be instrumental to further understand mural cell phenotypes.

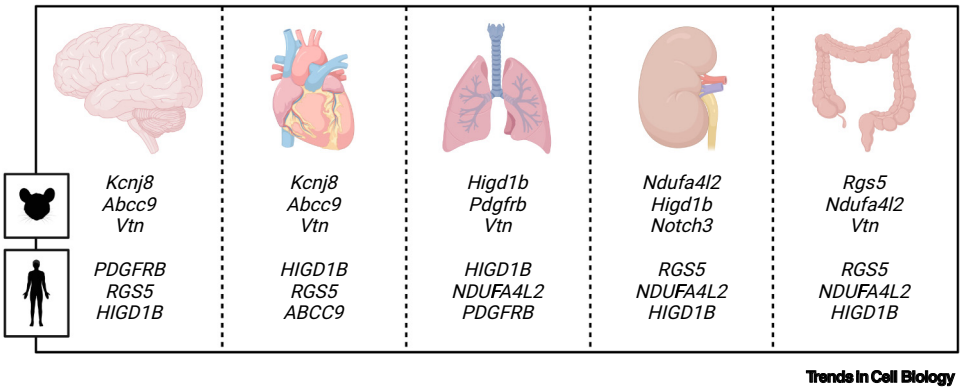

Figure 2. Organotypic heterogeneity of pericyte markers. This figure summarizes top-ranked pericyte markers in the brain, heart, lung, kidney, and colon of mouse (upper row) and human (lower row). Pericyte markers were chosen based on a stringent evaluation of transcriptional abundance, specificity, and homogeneity utilizing information provided by single-cell RNA sequencing (scRNA-seq) data [6–8,50,82,84,85,95,100–102]. Validation of the selected markers by *in situ* analysis was used as a second criteria for their selection.

Pericytes at play during vascular growth

Many studies have documented that pericytes contribute to angiogenesis [10]. The historical view proposes that pericytes mainly contribute to the late stages of vessel formation [2,10]. By taking advantage of the mouse retina as a paradigmatic experimental model of developmental angiogenesis, this concept has been challenged [11–16]. Indeed, these studies showed that, during the early phases of developmental angiogenesis, pericytes, which have not yet achieved the maturity seen in formed vessels, are permissive to cell-cycle progression, morphological adaptation, and migration [12,13]. In this setting, pericyte growth precedes the expansion of ECs, although it is still unclear why. One possibility is that, by expanding rapidly, pericytes ensure the production of sufficient EC growth signals, a hypothesis which is coherent with the observation that inhibition of pericyte activation blocks EC proliferation [12] and induces nuclear translocation of FOXO1 [11], the master regulator of EC quiescence [17]. Another study that examined the brain vasculature showed that, when pericytes are absent, ECs become angiogenic but are not able to proliferate [18], thereby supporting a model in which ECs require the presence of pericytes to expand. Nonetheless, it is fair to acknowledge that other studies have shown that reduced pericyte coverage leads to increased EC proliferation [19]. Although these discrepancies highlight that pericyte–EC interactions are complex, they may be explained by the differences between the animal models and genetic strategies used to interfere with pericytes. Importantly, pericyte behaviors during angiogenesis have been mostly described in tissues belonging to the CNS. Hence, given the high abundance of pericytes in the CNS, it is possible that angiogenic pericytes fulfill different roles in tissues where ECs substantially outnumber them. Another interesting observation is that, during angiogenesis, immature pericytes remain in close contact with ECs, although they do not cover them in their entirety [12,20]. This suggests that pericyte–EC communication during angiogenesis relies on both paracrine and juxtracrine signaling, and may explain why pericyte loss [11,16,21,22] and impaired transition to a fully maturate state [12] lead to distinct endothelial phenotypes during angiogenesis. scRNA-seq analysis of prenatal developing human brains confirmed that angiogenesis is supported by immature mural cells [20]. Consistent with mouse data [12], the state of mature human pericytes correlates with the progression of angiogenesis. Furthermore, the gene expression profiles of these cells show involvement in processes related to the transport across the **blood–brain barrier (BBB)** and the synthesis of ECM components [20]. Together, these data support a model in which pericytes modulate the early phases of angiogenesis by directly regulating EC behavior. Intriguingly, however, detailed ultrastructural

analysis of angiogenic vessels in human brain distinguishes only a single mural cell population, compared to three distinct EC populations [20]. This suggests that ultrastructural features do not define subtype specification in the mural cell compartment, and that molecular and structural features are not necessarily associated with each other.

Brain pericytes and vessel contraction: a matter of transitional phenotypes

Although the regulation of vascular tone through pericyte contractility is considered to be an important function of cardiac, renal, and pulmonary pericytes, as well as of HSCs [2], there has been a long-standing debate in the field as to whether pericytes actively modulate cerebral blood flow [23–25]. For instance, by using optical imaging, Hill *et al.* suggested that neural/glia antigen 2-positive ($NG2^+$) αSMA^- pericytes are not contractile and do not actively modulate the capillary diameter [26]. Instead, by similar optogenetic approaches Hartmann *et al.* proposed that pericytes do constrict, although they require prolonged and more intense stimulation than αSMA^+ mural cells located at larger vessels [27]. Although no consensus has been established, the opposing results between studies may simply reflect heterogeneities in the type of blood vessels and mural cells analyzed. A recent report has shown that $NG2^+\alpha SMA^+$ mural cells, located at the transitional segment between arteries and capillaries, regulate the vascular tone and contractility [28]. This suggests that the transition of functional phenotypes between mural cells covering distinct types of blood vessels is tightly regulated.

scRNA-seq analysis of brain mural cells has revealed an abrupt change in the molecular signatures of pericytes and mural cells located in arteries, even from cells residing in proximity on the vasculature, thereby supporting the existence of a blunt transition [6]. Taken together, one can speculate that, in addition to defined vSMC types, there is a subtype of mural cells that exhibit some traits, but not all, of classic pericytes, and are located at transitional vessels and can modulate the vascular tone. Given the ability of pericytes to adapt their phenotype to various microenvironmental conditions [1,2], it is also possible that regulation of blood flow may only occur under specific circumstances. However, one should consider that some of the data disputing pericyte contractility may relate to experimental artefacts, and it should be stressed that most analyses were conducted in the cerebral vasculature as a prototypical example of a vascular bed that is highly sensitive to contraction [25]. An important observation is that pericytes exhibit significant organotypic differences in the basal expression of contractility genes, and pericytes in the bladder and colon express considerable levels of *Myh11*, *Tagln*, and *Acta2* (αSMA), whereas pericytes in the brain, lung, and heart express negligible amounts of these contractile genes [6,7]. This highlights a conundrum regarding how brain pericytes regulate vessel contractility when typical contractility genes are not expressed.

Pericyte safeguarding the capillary brain bed by a special touch

An essential function of pericytes is to regulate the BBB by controlling the passage of fluid and substances into the parenchymal space [22,29]. Hence, defective pericyte coverage caused by pericyte dysfunction, impaired pericyte recruitment, and pericyte loss all lead to increased EC transcytosis and permeability [22,29]. Aberrant platelet-derived growth factor B (PDGF-B)/platelet-derived growth factor receptor beta (PDGFRβ) signaling is sufficient to experimentally reduce pericyte abundance and the subsequent loss of BBB properties [22,29]. In addition, proper ECM deposition by pericytes (among other cell types composing the neurovascular unit) plays an essential role in maintaining the integrity of the vascular barrier. Indeed, pericyte-derived vitronectin prevents endothelial transcytosis by binding to integrin α5 subunit on ECs [30], and pericyte-secreted laminin interacts with the dystrophin–glycoprotein complex in astrocytes and regulates their endfeet polarization [5,31].

To serve as guardians of the capillary bed, pericytes also establish physical interactions with ECs and form a continuous chain-like network along the capillaries of the cerebral vasculature. Adequate

coverage of the endothelium is sustained by active remodeling of distal pericyte processes through cytoskeletal rearrangements [32]. Of relevance, pericyte remodeling capabilities become exhausted with age [33], and this may explain why pericyte coverage is diminished in the vasculature of old mice [33,34]. An interesting observation is that pericyte depletion in adult mice leads to relatively mild BBB defects in different experimental models [35,36]. This includes adult induced *Pdgfb* ablation [36] and diphtheria toxin A (DTA) expression in PDGFRβ^{+} cells [35]. Currently it is not clear why loss of pericytes leads to different vascular barrier phenotypes in development and adulthood. Given that the BBB becomes functional during late embryonic development, one can speculate that defects in pericyte coverage are only significant before the onset of BBB formation. Another possibility is that pericyte coverage determines the threshold for BBB defects, and Vazquez-Liebanas *et al.* showed that only <50% longitudinal pericyte coverage in adult brains leads to significant leakage defects [36]. This is coherent with previous observations of brain vessel phenotypes during development which demonstrated that pericyte coverage is positively correlated with BBB integrity [22]. Choe *et al.* also reported that DTA-induced loss of pericytes leads to **capillary stalling** due to increased interactions between ECs and leukocytes. However, because this effect was not observed in other adult pericyte depletion models [35], one should acknowledge that it is possible that the expression of DTA generated unintended toxic effects beyond pericytes.

Pericytes in disease

Pericyte dysfunction is a hallmark of various diseases (Figure 3). For a long time it was believed that maladaptive pericytes mainly affect vascular homeostasis because pericyte and EC functions are interdependent and require bidirectional communication (Box 2). However, there is growing evidence that pericytes have roles in processes beyond the vasculature. As such, pericyte-derived signals (hereafter referred to as **pericrine signaling**) also modulate tissue function in both physiology and disease. In the following section, we capture recent data showing new observations that link pericyte dysfunction and loss in vascular and non-vascular-related diseases.

The CNS: a hotspot of pericyte-related vascular diseases

Pericyte-related vascular defects have been reported in various CNS diseases, including Alzheimer's disease (AD), Parkinson's disease, dementia, stroke, diabetic retinopathy, glaucoma, and intracranial vascular malformations [5,37–39]. The involvement of pericytes in several CNS-related diseases is partially explained by their abundance within the brain vasculature and their key role in maintaining the BBB, where barrier breakdown precedes neurodegeneration. Other phenotypes linking pericytes dysfunction and CNS disease include neuron death [40] and impaired **neurovascular coupling** [41,42]. Intriguingly, NG2^{+} retinal pericytes orchestrate neurovascular coupling through closed-ended nanotubes between pericytes on adjacent capillaries, even when they are positioned far apart. These nanotubes terminate in a gap junction at the recipient pericyte, which permits rapid fluxes of small molecules and calcium ions, thereby allowing pericytes to coordinate neuronal activity [41]. Indeed, maintaining adequate calcium levels is essential to sustain pericyte function in the CNS, and aberrant levels of calcium in NG2^{+} pericytes lead to poor recovery after ischemic stroke [23,43] or neovascular dysfunction and neuronal death in glaucoma [42].

AD is the prototypical example of a CNS disease associated with aberrant vascular function and BBB breakdown linked to pericyte dysfunction and loss [38,44]. Although the involvement of pericytes in AD has been recognized for several years [5,44], new insights have challenged the timeframe in which patients suffering from AD develop pericyte dysfunction and BBB impairment. Indeed, it is now understood that BBB breakdown is an early event in AD, and these defects are used as an early biomarker of cognitive decline [45]. We highlight recent observations which

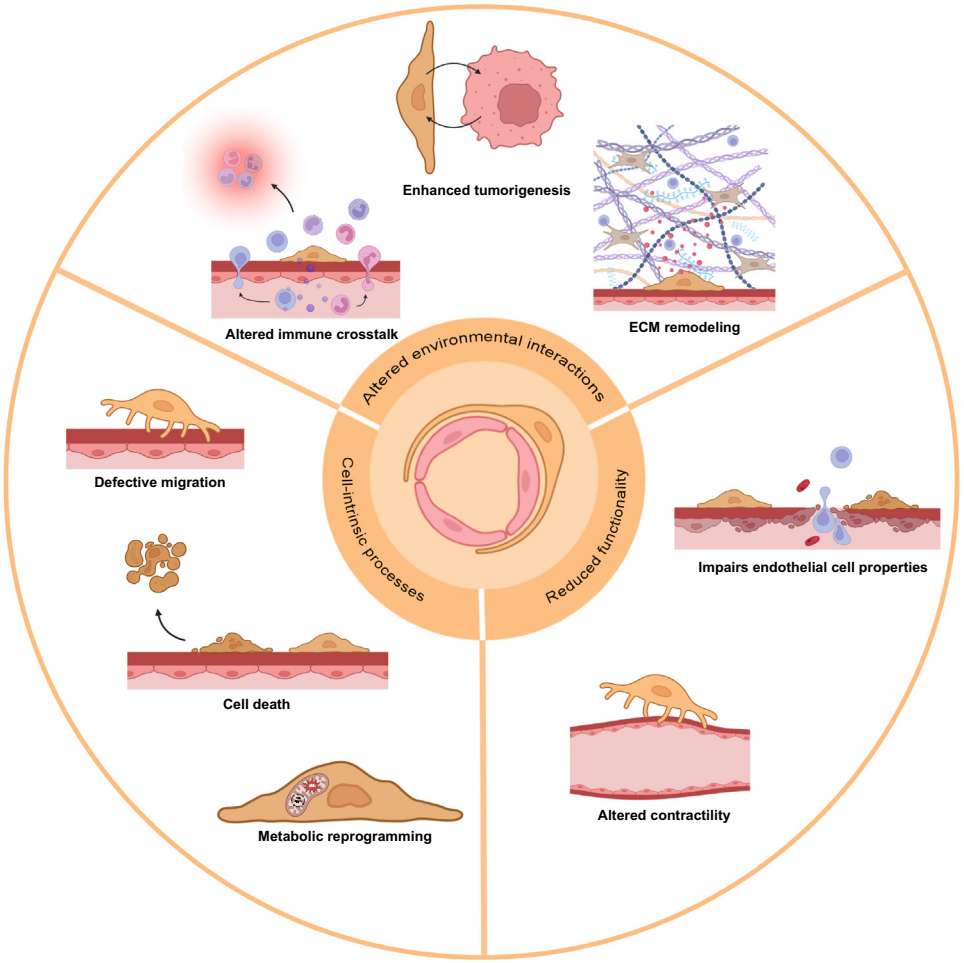

Figure 3. Dysfunctional pericytes in disease. This figure illustrates a compendium of pathological features associated with pericytes which have been shown to contribute to disease onset/progression. Alterations include cell-intrinsic processes (cell death, defective migration, and metabolic reprogramming), reduced functionality (increased transcytosis and altered contractility), and altered environmental interactions [extracellular matrix (ECM) remodeling, immunomodulation, and enhanced tumorigenesis].

Box 2. Key signaling pathways that orchestrate pericyte–EC crosstalk

Given the close relationship between pericytes and ECs, it is not surprising that bidirectional communication and regulation between them are crucial during vessel formation and maintenance. During angiogenesis, established examples of pericyte–EC communication include the PDGFRβ, transforming growth factor β1 (TGF-β1), ANG1, and NOTCH3 pathways [1]. PDGF-B production from tip ECs is the master signal that recruits PDGFRβ-expressing pericytes to newly formed vessels [1], together with CD146 (MCAM), which acts as a coreceptor for PDGFRβ [96]. Recent advances have shown that NCK1 and NCK2 promote phosphorylation of PDGFRβ in response to PDGF-BB and stimulate pericyte migration by inducing MRTF translocation to the nucleus where they interact with the serum response transcription factor (SRF) [13,21]. Similarly, jagged 1 (JAG1) expressed by ECs activates NOTCH3 in pericytes and promotes pericyte maturation [14,97] and the expression of PDGFRβ [98]. Conversely, ANG1 is secreted by pericytes, activates the tyrosine receptor TIE2 in ECs, and promotes EC maturation and vascular integrity [2,15]. TGF-β exerts complex effects on ECs and pericytes, and TGF-B receptor 1 (also known as ALK5) plays a dominant role in these interactions. Indeed, deletion of ALK5 in ECs leads to pericyte dysfunction and hemorrhagic vascular malformations [99]. Instead, deletion of ALK5 in pericytes results in increased EC proliferation, reduced collagen deposition, and enhanced matrix metalloproteinase activity [19]. Of note, pericytes also express canonical EC receptors such as VEGF-R1 [15,16] and TIE2 which allow pericytes to modulate intrinsic EC signaling.

support the involvement of pericytes in the onset of AD. For instance, Nortley *et al.* showed that the reduction in cerebral blood flow, that is considered to be the first clinical manifestation of AD, is caused by amyloid-β-induced pericyte contraction in brain capillaries [46]. Another study indicated that cognitive decline and BBB disruption in AD are linked to accelerated pericyte degeneration in carriers of AD susceptibility allele apolipoprotein E4 (*APOE4*) [47], a process which occurs independently of amyloid-β pathology. In this context, *APOE4* carriers show high baseline cerebrospinal fluid levels of soluble (s)PDGFRβ which can be used as a BBB pericyte injury biomarker [47]. Intriguingly, analysis of the cortex of *APOE4* transgenic mice using single-nucleus (sn)RNA-seq and phosphoproteomics revealed profound molecular changes related to progressive BBB failure in both ECs and pericytes [48]. Nonetheless, because only a constitutive *APOE4*-expressing transgenic line was included in the study, it remains unclear whether the molecular alterations of ECs and pericytes solely comprise cell-autonomous effects. In addition, one should not forget that mice do not fully recapitulate all traits of AD. It has been recently noted that pericytes and microglia associations (described in both physiological mouse and human brains) are diminished in the brain capillaries of individuals with AD, and this may also have implications for BBB breakdown [49]. In human brain, two types of pericytes have been identified that are distinguished by solute transport and ECM organization (Box 1). Intriguingly, the second type seems to be selectively affected in AD [50]. Thus, identifying methods to specifically target this cluster of pericytes may provide new ways to maintain vascular fitness in AD.

Pericyte degeneration and death also encompasses early phases of diabetic retinopathy, in which pericytes are primary targets of hyperglycemic damage. Recent findings suggest that, upon initiation of hyperglycemia, pericytes shift towards cell-bridging positions, resulting in physical detachment from ECs [51]. Whether this remodeling is independent of pericyte death or is related to the initiation of that process needs further investigation. Mechanistically, pericyte detachment and shifting are induced by exogenous factors such as angiopoietin 2 (ANG2) and PDGF-B, and are reversed by insulin treatment, illustrating the dynamic behavior of pericytes in the microvasculature [51,52]. In line with this, PDGFB signaling through PDGFRβ and NCKs in pericytes that cover sprouting vessels during experimental proliferative retinopathy [oxygen-induced retinopathy (OIR) model] activates ectopic αSMA expression and promotes pathological neovascularization [21]. Interestingly, depletion of retinal pericytes in adulthood does not phenocopy retinopathy unless another stimulus is present (e.g., vascular endothelial growth factor A, VEGF-A). Upon depletion of pericytes, either during vessel development or in adulthood followed by VEGF addition, inhibition of ANG2 action restrains the severity of the diabetic retinopathy-like phenotypes [11]. Molecular effectors governing the early phases of diabetic retinopathy have remained elusive, precluding the development of drugs aiming to halt disease onset. These data suggest that targeting pericyte adhesion and migration capacities may be of therapeutic interest. Furthermore, pericyte loss in diabetic retinopathy was recently associated with aberrant levels of circular RNAs [53], thereby suggesting the use of circular RNAs as a diagnostic biomarker for early pericyte dysfunction in disease.

Finally, we would like to stress that familial mutations in essential pericyte genes have also been linked to CNS abnormalities. Well-known examples include loss-of-function mutations in *NOTCH3* as a cause of **CADASIL** [54], and mutations in *PDGFRB* as a cause of brain calcifications [55], neurological deterioration, and white matter lesions [56]. Of note, these genes are equally relevant for pericyte and vSMC biology, and it is unclear whether these mutations lead to distinct phenotypes in mural cells. Current next-generation sequencing approaches allow the discovery of somatic mutations present in pericytes at low allelic frequency. In line with this, it has been proposed that *PIK3CA*- and *AKT*-related somatic cerebral cavernous malformations in mice emerge from mutant pericytes [39,57]. However, these data have some caveats because

the lineage-tracing experiments used to support these findings were performed with a CRE-recombinase mouse line that is neither pericyte-specific nor inducible.

Pathobiological pericytes beyond the CNS

Although the implications of pericytes in diseases beyond the CNS are less well studied, the number of diseases demonstrating the involvement of pericytes continues to expand. We discuss here emerging evidence supporting a relevant role of pericytes in myocardial infarction [58], acute lung injury [59], and diabetes [60] as prototypical examples. For instance, after myocardial infarction, pericytes regulate inflammation and immune cell trafficking, and modulate ECM remodeling and revascularization [61]. In line with this, molecular reprogramming of PDGFRβ^{+}NG2^{+} cardiac pericytes into vSMCs through inhibition of MEK1/2 improved the functional cardiac response by promoting revascularization [58]. In acute lung inflammation, the crosstalk between endothelium-derived nitric oxide (NO) and pericyte soluble guanylate cyclase (sGC) is impaired, leading to elevated vascular permeability [59]. Pharmacological activation of the NO–sGC axis led to an improved pericyte-driven inflammatory response. Moreover, pericytes in pancreatic islets exert vascular control of hormone secretion and glucose homeostasis, and pericyte alteration has been linked to diabetic islet dysfunction [60]. Interestingly, pericyte effects on islet functionality are not limited to vascular support for insulin secretion because pancreatic β cell maturation and functionality rely on pericyte-derived bone morphogenic protein 4 (BMP4). Recently, other pericrine signaling molecules have been identified as key players in the functional regulation of tissue parenchyma encompassing a range of organ-specific functions in both vascular and non-vascular interfaces. Two interesting examples are that leptin receptor-expressing pericytes in the mediobasal hypothalamus mediate energy balance via neuronal leptin signaling [62], and that the Hippo–YAP/TAZ pathway in pericytes generates essential pericrine signals to epithelial and ECs during lung morphogenesis [63]. All things considered, these studies suggest that restoring the physiological functions of pericytes improves blood vessel performance and disease outcomes in various contexts, which may encourage the development of novel pericyte-focused therapies.

Tumor pericytes: loss or change of identity?

Many preclinical studies over the past decade showed that pericyte dysfunction is involved in cancer progression [64]. In this context, it is now well established that tumoral vessels are poorly covered by pericytes [65,66], that diminished pericyte recruitment and maturation lead to enhanced vascular and tumor growth [15,66], and that pericyte depletion favors metastasis. However, there is no consensus about whether defective pericyte–EC interaction in tumors relates to loss of pericyte molecular identity [67], pericyte transdifferentiation into fibroblasts [68], poor pericyte recruitment [66], or a combination of these phenotypes. Functionally, metabolic reprogramming of tumor pericytes has also been implicated in abnormal blood vessel contraction and unfavorable patient outcomes [69].

scRNA-seq analyses have provided a new layer of information about tumor pericytes by showing that tumor pericytes are, in fact, relatively homogeneous [70–72]. However, one should acknowledge that most tumor scRNA-seq datasets include low numbers of pericytes, and the presence of tumor pericyte subclusters may have been obscured by the granularity of the data. One way to overcome this limitation would be to establish spatially resolved pericyte-focused atlases by using multiomic approaches. An interesting observation is that pericyte phenotypes are distinct depending on the mechanisms by which tumor vessels form. While angiogenic pericytes persist in an active immature state characterized by a signature of motility and ECM organization, pericytes covering **co-opted vessels** remain largely quiescent [71,73]. Together, these studies support a model in which pericytes undergo genetic and molecular reprogramming in cancer,

which in turn has negative consequences for disease progression. Nonetheless, one should not forget that most of these data refer to mouse preclinical studies, and adequate longitudinal studies in humans are missing. Of note, the so-called pericrine signaling response is also at play in cancer. Indeed, in hepatocellular carcinoma it has been shown that metabolic reprogramming in tumor cells activates HSCs which in turn promote tumorigenesis through the secretion of senescence-associated factors [74]. Another study has described that loss of integrin β3 in tumor pericytes leads to enhanced focal adhesion kinase (FAK)-mediated cytokine release by pericytes, which subsequently stimulates tumor survival and growth [75].

Pericyte immunomodulatory properties

Emerging evidence suggests that pericytes form an integral part of the immune surveillance unit rather than solely performing complementary functions. Upon proinflammatory stimuli, pericytes promote endothelial expression of the leukocyte adhesion molecules vascular cell adhesion protein 1 (VCAM-1) and/or intracellular adhesion molecule 1 (ICAM-1) in the CNS, lung, skin, or muscle that subsequently promote T cell or macrophage infiltration into the affected tissue [59,76,77]. The *Rgs5*$^{+}$ and *Col1a1*$^{+}$ subgroups of PDGFRβ^{+} perivascular cells seem to be early responders to neuroinflammation [78]. Of note, inflammation *per se* induces pericyte detachment from the endothelium and impairs barrier properties [59]. In addition to the physical interaction with leukocytes, pericytes also secrete and respond to cytokines that further regulate immune cell functions, including both innate and adaptive responses. The chemotactic migration and effector functions of neutrophils, T cells, and macrophages are dependent on these early pericrine signals, including MIF, CXCL1, and CCL2 [77–80].

It is now believed that modulation of the immune-related functions of pericytes could affect the outcome of disease progression. For example, pericyte-deficient *Pdgfb*$^{ret/ret}$ mice exhibit increased leukocyte infiltration and activation, leading to aberrant inflammation in a model of experimental autoimmune encephalomyelitis [76]. Treatment with antagonistic VCAM-1 and ICAM-1 antibodies partially rescued the excessive inflammatory phenotype in *Pdgfb*$^{ret/ret}$ mice. Similarly, activating sGC in acute lung injury improved disease outcomes by increasing pericyte interaction with ECs [59]. Conversely, in the tumor microenvironment, tumor cells induce autophagy of NG2^{+} pericytes which equips them with immunosuppressive properties that favor tumor cell survival and prevent antitumor T cell responses [81]. Pericytes have also been implicated in the underlying pathophysiology of emergent infectious diseases such as coronavirus disease 2019 (COVID-19) [82], thus presenting an additional niche of investigation for the field in the coming years. In conclusion, the importance of pericytes during various inflammatory processes is growing in recognition, although the modulation of immunity by pericytes can have double-edged outcomes.

Do pericytes contribute to fibrosis?

A dysregulated tissue repair response after acute or chronic injury can lead to the onset of fibrosis associated with the abnormal accumulation of activated and contractile αSMA^{+} myofibroblasts [83]. Myofibroblasts secrete high amounts of inflammatory mediators, growth factors, and ECM components, and promote aberrant ECM remodeling. The current consensus places fibroblasts as the predominant origin of myofibroblasts, although various studies have found alternative cellular origins [83]. Indeed, the existence of pericyte-to-myofibroblast transition has been proposed as a contributing factor in several fibrotic contexts [2], but the promiscuity of cell markers within the mesenchymal compartments across tissues has led to ambiguous and contradictory observations. In the latest developments, scRNA-seq, ATAC-seq, and spatial transcriptomics provide new insights into this conundrum which support a pericyte origin of myofibroblasts in the fibrotic liver, colon, and kidney. For instance, central vein-associated *Rgs5*$^{+}$ HSCs are thought to be the dominant origin of ECM-producing myofibroblasts in fibrotic mouse liver [84]. In human colorectal

cancer, a subset of periostin (*POSTN*)$^+$ myofibroblasts seem to originate from *RGS5*$^+$ pericytes [70]; similarly, *NOTCH3*$^+$*RGS5*$^+$*PDGFRβ*$^+$ human pericytes contribute to the generation of *POSTN*$^+$*PDGFRα*$^+$*NKD2*$^+$ myofibroblasts during kidney fibrosis [85]. Surprisingly, however, the same authors did not capture the existence of profibrotic pericytes during myocardial infarction when sequencing the entire heart [86]. Although transdifferentiation from pericytes to myofibroblasts may be tissue-specific, it is fair to acknowledge that the latter study did not include pericytes in the trajectory analysis that predicted the origins of myofibroblasts.

Lineage-tracing experiments in mice have also cast some light onto the role of pericytes in fibrosis. For instance, Pham *et al.* showed that myofibroblast genes are enriched in *Tbx18*$^+$ pericytes from injured mouse hearts and brains [87], and Dias *et al.* reported that GLAST$^+$PDGFRβ$^+$ perivascular cells also contribute to fibrosis in the post-stroke brain [88]. In line with this, depletion of GLAST$^+$PDGFRβ$^+$ perivascular cells in the spinal cord leads to reduced fibrotic scar after injury and improves neuronal function [89]. Of note, GLAST$^+$PDGFRβ$^+$ perivascular cells were characterized as spinal cord pericytes by the researchers, but there is insufficient evidence to rule out that these cells might be fibroblasts or astrocytes. This further exemplifies that the shared marker expression profiles of pericytes and other perivascular residing cells still hamper the design of robust pericyte reporter models. Moreover, multiple studies have found no significant pericyte origin for myofibroblasts in distinct fibrosis models of the CNS [90,91] and heart [92]. Although the discrepancies between studies may reflect the lack of robust pericyte identification strategies, it appears that the occurrence of pericyte-to-myofibroblast transition is tissue-specific, and is contingent both on the local microenvironment and on the extent of the injurious stimuli [83]. This emphasizes the need to further unravel the fibrotic pericyte responses in different organs and prompts the question of how myofibroblast origins relate to different pathophysiological phenotypes. All things considered, the origin of myofibroblasts may involve distinct precursor cells depending on the circumstances, although a role for pericytes seems to be indisputable (Figure 4).

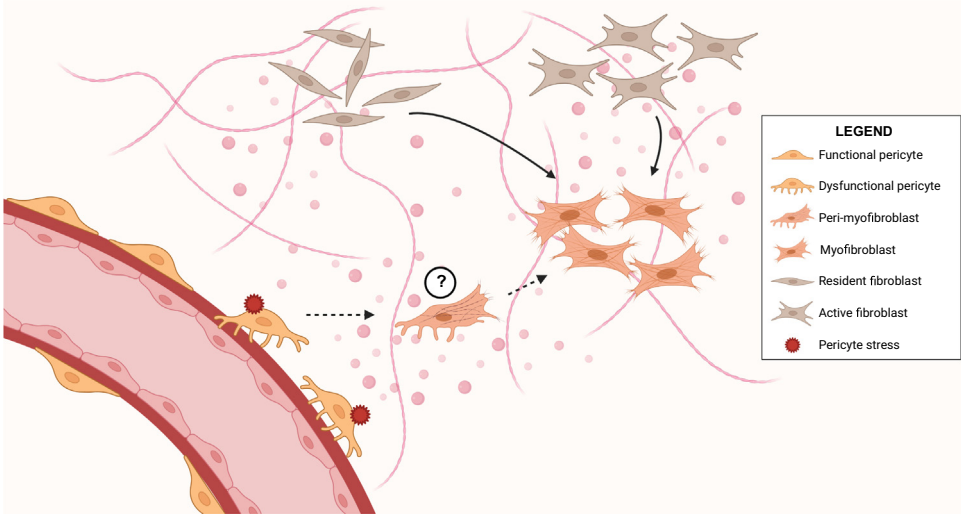

Figure 4. Pericytes as a source of myofibroblasts in fibrosis. Schematic illustration showing how, under stress conditions, pericytes detach from vessels and undergo a transition towards highly contractile, extracellular matrix (ECM)-producing myofibroblasts. The relative contributions of pericytes versus fibroblasts in a given context remains a topic of ongoing debate and investigation. Pericytes and fibroblasts may play different roles in fibrosis depending on several factors, including the anatomical location, local microenvironment, source of injurious stimuli, and technical biases.

Concluding remarks

It is widely recognized that pericytes play an important role in blood vessel formation, stabilization, and function, and that degeneration or loss of brain pericytes impairs their protective barrier properties. Recent advances have revealed novel and crucial roles for pericytes across tissues in a variety of vascular and non-vascular processes. Single-cell technology is becoming more commonly used to better understand the molecular processes that define pericytes in health and disease. Although the molecular and functional attributes of pericytes are not fully elucidated, deep sequencing has revealed organotypic pericyte heterogeneities and new criteria to distinguish pericytes from other cell types. Despite the numerous suggested roles of pericytes in various diseases and physiological processes, including neurodegeneration, cancer, fibrosis, blood flow regulation, and inflammation, the underlying organotypic mechanisms of these contributions are not yet fully understood. The discrepancies between some studies highlight the importance of designing suitable mouse models for evaluating the specific mechanisms by which pericytes impact on these processes, and future cross-validations with human data are warranted to ascertain the clinical relevance of pathological pericytes (see Outstanding questions). Overall, based on the emerging evidence on the contribution of pericytes to several diseases, we anticipate an increasing emphasis on pericyte-oriented research in vascular (and non-vascular) studies in the coming years.

Outstanding questions

Why are pericytes molecularly and functionally promiscuous and heterogeneous between distinct tissues? If the transcription factors that regulate pericyte differentiation and function are similar across tissues, will epigenetic mechanisms provide cues into the mechanisms of pericyte identity?

Will spatial molecular atlases focused on pericytes address the key functional and identity conundrums posed by transitioning phenotypes? Will this suffice, or are complementary morphological and functional studies also necessary?

Will pericyte-focused therapy provide new means to stimulate functional angiogenesis in pathology? Given that pericytes are associated with many diseases, will (and how broadly can) pericyte-focused therapies improve patient outcomes?

Neurodegenerative diseases are age-related diseases, and pericyte degeneration is an aging process. Hence, is pericyte degeneration a confounding factor in the development of age-related neurodegeneration? Will maintaining healthy pericyte function promote healthy aging?

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Declaration of interests

The authors declare no conflicts of interest.

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