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Pericytes at the intersection between tissue regeneration and pathology

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Abstract

Perivascular multipotent cells, pericytes, contribute to the generation and repair of various tissues in response to injury. They are heterogeneous in their morphology, distribution, origin and markers, and elucidating their molecular and cellular differences may inform novel treatments for disorders in which tissue regeneration is either impaired or excessive. Moreover, these discoveries offer novel cellular targets for therapeutic approaches to many diseases. This review discusses recent studies that support the concept that pericyte subtypes play a distinctive role in myogenesis, neurogenesis, adipogenesis, fibrogenesis and angiogenesis.

Keywords

injury; pericyte; regeneration; stem cell

INTRODUCTION

In the late 1800s, the French scientist Charles-Marie Benjamin Rouget described a population of contractile cells in the capillaries, which were named after him [1]. Fifty years later, Karl Wilhelm Zimmermann renamed them pericytes because they were primarily located around microvessels [2]. Microvascular pericytes have long projections that encircle the vessel wall in almost all tissues and organs [3]. They communicate with endothelial cells along the length of the vessel by physical contact and paracrine signalling [4].

Until recently, light and electron microscopy were the only techniques able to visualize them, and pericytes distinct from vascular smooth muscle cells, perivascular fibroblasts, juxtavascular microglia and other perivascular cells could not be identified precisely,

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resulting in the still widely held notion that their physiological function is limited to supporting microvessel stability.

In previous years, however, pericytes have been isolated successfully from a variety of organs and established in tissue culture [5,6]. Rapidly expanding insights into their physiological functions have attracted the attention of many research groups. Approaches that combine genetic lineage tracing, anatomical location and expression of surface markers now enable a clearer understanding of pericytes' varying roles in health and disease.

PHYSIOLOGICAL FUNCTIONS

Previous studies have shown that, in addition to physically stabilizing vessels, pericytes regulate blood flow [7-9]. They participate in vascular development, maturation, remodelling, architecture and permeability [10-14]. They collaborate with astrocytes to maintain the functional integrity of the blood–brain barrier [15-25]. Pericytes affect blood coagulation [26-28] and immune function by regulating lymphocyte activation [29-32]. Evidence for phagocytic properties has been reported [33-37]. We invite the reader to consult recent publications that detail these pericyte functions [38-43]. In the present review, we will discuss studies that identify pericytes as stem cells that participate in tissue formation and regeneration.

HETEROGENEITY

Pericytes are heterogeneous in terms of phenotype, distribution and origin [43-45]. In 1923, Zimmerman was the first to distinguish three varieties according to their location in the blood vessels: pre-capillary, true-capillary and post-capillary [2]. Pre-capillary pericytes have circular branches that wrap themselves around the vessel and express varying amounts of α-smooth muscle actin (αSMA) [46]. True-capillary pericytes are spindle-shaped, highly elongated, extending mainly along the vessels' long axis, and have short secondary processes. They do not express αSMA protein [46]. Post-capillary pericytes cover the abluminal surface of post-capillaries and are shorter and stellate.

Pericyte coverage of blood vessels also differs by organ. The ratio of pericytes to endothelial cells is approximately 1:1 in the central nervous system (CNS) and retina, 1:10 in the lung and skin and only 1:100 in skeletal muscle [47]. This variation may be linked to the tissue's function. One study proposed that the more pericytes, the higher the blood pressure in the organ, and the greater blood vessel control [47], which could explain why more pericytes surround larger diameter vessels [44].

Pericytes also differ in their embryonic origin. Lineage tracing studies indicate that pericytes in the cephalic region are of neuroectodermal origin [48]. In most other organs, pericytes derive from the mesoderm; specifically, the sclerotomal compartment [49-56]. However, given their heterogeneity within and between tissues, their exact origin remains unclear.

The strategy used to identify pericytes combines their anatomical location in very close relationship between blood vessel endothelial cells and marker expression. However, not all pericytes express all the markers, nor are all markers found exclusively in pericytes.

Therefore, various markers and cell location must both be identified to distinguish pericytes from other cells, including fibroblasts. For example, pericytes and fibroblasts express platelet-derived growth factor (PDGF) receptor-β (PDGFRβ) [57,58], but pericytes do not express fibroblast-specific protein 1 (FSP1) [59] or scleraxis [60-62]. Thus, PDGFRβ^+ cells that express FSP1 and/or scleraxis are fibroblasts, and those that do not and are located around CD31$^+$ blood vessels are pericytes. Markers used to identify pericytes include αSMA [63], PDGFRβ [14,64], aminopeptidase N (CD13) [65], nerve/glial antigen-2 (NG2) proteoglycan, also called chondroitin sulfate proteoglycan 4 (CSPG4) [66], and many others [67]. Their expression profiles also confirm pericyte heterogeneity. Pericytes localized on venules express desmin and αSMA, whereas those on capillaries express desmin but are usually negative for αSMA [67,68]. The ATP-sensitive potassium-channel Kir6.1 is undetectable in pericytes in the skin and heart but highly expressed in brain pericytes [69]. Spinal cord pericytes that express the glutamate aspartate transporter (Glast) differ from those that express desmin and αSMA [70]. Two distinct types of nestin–GFP$^+$ pericytes express either high or low levels of GFP in the bone marrow [71]. Bone marrow sinusoid-associated leptin receptor (LEPR)$^+$ pericytes are distinct from LEPR$^-$ pericytes [71]. Skin NG2$^-$ and NG2$^+$ pericytes have been described [72]. We distinguished two populations of pericytes in the skeletal muscle based on intron-II–nestin–GFP expression [73]. Their roles in specific tissues are described below.

Pericytes are relatively undifferentiated connective tissue cells associated with small blood vessel walls. Their cross-talk with other cells promotes tissue survival [74]. They are similar to mesenchymal stem cells (MSCs) and can be obtained from several organs [75]. Because blood vessels are distributed in almost all organs, pericytes are thought to be MSCs [75,76], and they locate within the niche [77] and share markers *in vivo* and *in vitro* [76] with MSCs. Moreover, cell isolation followed by long-term culture provides compelling evidence that the origin of MSCs is perivascular [5,78-88]. Pericytes may differentiate along distinct lineages depending on their location and physiological state [5,73,76-80,82-113]. They have been shown to improve heart function following myocardial infarction in animal models [114,115] and to form skeletal muscle [80,85], dental tissues [87,116], follicular dendritic cells [117], fat [85], cartilage [118] and bone [119]. They accelerate wound healing [120] and contribute to fibrous tissue formation [121,122]. Their role in forming and stabilizing engineered blood vessels [123] supports their use in vascular therapy. Pericytes can be reprogrammed to develop neuronal cells [91]. Finally, they may be involved in tissue regeneration as ‘niche cells’ for specialized stem cells, as documented for haematopoiesis [71,124-126].

Below we will examine recent reports on pericytes’ role in tissue regeneration and regenerative medicine.

PERICYTES AND MYOGENESIS

Previous studies indicate that pericytes contribute to skeletal muscle formation [126a]. After xenographic transplantation, both freshly sorted and long-term cultured pericytes colonize host muscle, spontaneously fuse together with myoblasts to form myotubes [88], and help to regenerate muscle in cases of acute injury or chronic muscle necrotic disease, such as

muscular dystrophy [88]. Some researchers propose that they generate satellite cells, the *bona fide* muscle stem cells. After muscle injury, a small percentage of transplanted pericytes localize beneath the myofibre's basal lamina and express Pax7, indicating that they can occupy the satellite cell niche in skeletal muscle [80]. This myogenic potential can be generalized to pericytes residing in other tissues [85]. Since they can be cultured *in vitro*, pericytes are promising candidates for future cell-based therapies to treat muscular dystrophies [127].

Recently we reported two *bona fide* pericyte subpopulations, type 1 (nestin–$GFP^{-}/NG2^{+}$) and type 2 (nestin–$GFP^{+}/NG2^{+}$), in the skeletal muscle interstitium. They express the pericyte markers NG2, PDGFRβ and CD146, and are associated with blood vessels. Type 2, but not type 1, forms myotubes in culture. We demonstrated that after injury, only type 2 pericytes participate in muscle regeneration, forming myofibres *in vivo* [128]. Whether transplanting type 2 pericytes will improve physiological performance and skeletal muscle repair and regeneration remains to be elucidated.

Similar to what has been shown for other potential cell therapies [129-131], type 2 pericytes' regenerative capacity is affected by the host microenvironment; after injection in older host animals, they generate fewer and smaller myofibres [62] and any future therapies will have to consider tissue context. Recombination-based lineage-tracing technologies are helping to determine the contribution of type 2 pericytes and other cell types to myogenesis, but tracking pericyte fate *in vivo* will require the discovery of new markers that are expressed exclusively in a pericyte subpopulation.

Future studies must also determine whether the depletion of type 2 pericytes compromises tissue regeneration. Without satellite cells, muscle regeneration fails [132-135], and their interaction with endothelial cells [136] and connective tissue fibroblasts [134] is necessary for efficiency. Dying satellite cells release factors that may directly compromise pericytes' myogenic capacity. Pericytes may also require physical contact with satellite cells to induce muscle regeneration. Thus, ablating type 2 pericytes will be crucial to determining their role in muscle regeneration.

PERICYTES AND ADIPOGENESIS

Richardson et al. [137] showed that rat adipose tissue pericytes can convert into adipocytes *in situ* in response to thermal injury induced by an incandescent wire. These morphological observations led to the hypothesis that pericytes can be adipocyte progenitors [138] but do not constitute definitive proof. A close relationship between vascular growth and adipogenesis *in vivo* [139,140] suggests that vascular cells may function as adipocyte progenitors. More recently, pericytes cultured in adipogenic conditions accumulated lipid droplets in their cytoplasm and expressed peroxisome-proliferator-activated receptor-γ (PPARγ), an adipocyte-specific transcription factor. This result was also described *in vivo* but not for endothelial cells [118]. Ectopic fat production by vascular cells has been associated with atherosclerosis [141].

Early studies revealed that new adipocytes form along the vasculature [142], linking vascularization and fat formation [143], and suggesting that adipogenic progenitors reside in

the perivascular niche [144]. Findings from several studies strongly suggest that adipogenic progenitors are perivascular [86,145-147]. A 2008 study showed that vessel-associated PPARγ^+ cells express the pericyte markers PDGFRβ, NG2 and αSMA. Using the inducible genetic lineage-tracing system (*PdgfRβ*-CRE/Rosa-*LacZ* mice), the authors demonstrated that PDGFRβ^+ cells form adipocytes after transplantation [148]. Pericytes from various tissues differentiate into fat cells; for example, in skin and skeletal muscle cells when cultured under adipogenic conditions [85,149]. In a recent study [128], we reported that in skeletal muscle, adipogenic potential is restricted to type 1 pericytes, and only type 1 pericytes express the adipogenic progenitor marker PDGFRα. We also found that unlike type 2, type 1 pericytes cannot form muscle cells in response to muscle injury. In contrast, they contribute to fat infiltration in diseased skeletal muscle in such disorders, as obesity, dystrophies and aging [128]. As other cells are also involved in fat formation [59,150-157], the contribution of pericytes to adipose tissue accumulation must be quantified. So far, it has been described only in skeletal muscle. Whether they contribute to fat deposits in other organs, such as blood vessels, leading to atherosclerosis, is not known. Furthermore, monitoring the relative abundance of pericyte subtypes over time will clarify their correlation with increasing fat deposition in skeletal muscle with aging [158-161]. Future mechanistic studies should reveal how to block adipogenic (type 1) pericytes without affecting myogenic (type 2) pericytes.

PERICYTES AND NEUROGENESIS

The brain is one of the most vascularized organs [162]. Neurogenic cells are located very close to blood vessels, wrapping them in intricate processes [163-165]. Periventricular blood vessels develop at the onset of cortical neurogenesis [166]. Pericytes have a higher density in the brain compared with other organs [167] and play several roles in the CNS microenvironment; for example, they produce neurotrophins that provide neuroprotection under hypoxic conditions [168].

Pericytes migrate in response to traumatic brain injury [169]. The first evidence of their neurogenic potential was a study in the monkey hippocampus that showed neural differentiation of pericytes after ischaemia [170]. Rat brain primary pericytes can generate neurospheres [93,94] in the neuronal, astrocytic and oligodendrocytic lineages, and the process is faster in co-culture with endothelial cells [93] supporting the suggestion that endothelial cells provide trophic support to neurogenic activity [164]. A more recent study reported this neurogenic potential *in vitro* in human brain-derived pericytes [171].

Pericytes isolated from cerebral cortex can be converted into postmitotic functional neurons *in vitro* by direct cell reprogramming [91]. We do not know whether they can be directly reprogrammed *in vivo*, as recently shown for glial cells [172-174]. To confirm the apparent neural progenitor activity of pericytes throughout the CNS in response to ischaemia *in vivo* [107], genetic cell tracking will be required. Note also that non-CNS pericytes from the aorta [175] and fat [106] can be induced to neural differentiation [106,175].

In our recent work, we found that not all skeletal muscle pericytes can differentiate into neural progenitors under the same culture conditions. Type 1 pericytes generate α-SMA$^+$

pericytes but not neural cells. In contrast, type 2 pericytes generate neural progenitors that resemble brain NG2−glia in optimized culture conditions; when cultured alone, they become α-SMA$^+$ pericytes and do not form neural cells [73]. The counterpart of NG2−glia cells in skeletal muscle are Schwann cells, but whether pericytes can form Schwann cells is not known. Future studies will explore whether a particular pericyte subpopulation is the source of myelinating and/or nonmyelinating Schwann cells.

Other questions include whether organs apart from skeletal muscle have pericytes that cannot be induced to neural lineage; whether only type 2 pericytes in the CNS have neurogenic potential; and whether, *in vivo*, endogenous pericytes transform into neuron, astrocyte or oligodendrocyte progenitors in response to neurodegenerative disorders or trauma. Some studies indicate that although one pericyte subpopulation contributes to scar formation, another contributes to neural regeneration in the injured spinal cord [70]. Determining the exact functions of pericyte subpopulations may provide new cellular targets for pharmacological manipulation and new ways to improve repair in several CNS diseases.

PERICYTES AND TISSUE FIBROSIS

Previous findings suggest that pericyte participation in fibrosis is organ-dependent. In the liver, pericytes are also called Ito or hepatic stellate cells and reside in close contact with vascular endothelial cells [176,177]. Early studies indicating that they play a central role in hepatic fibrosis by producing collagen [178,179] were confirmed using collagen–GFP transgenic mice [180] and in a recent lineage-tracing study [181]. The authors generated pericyte-specific, lecithin-retinol acyltransferase (Lrat) Cre mice, which marked nearly all pericytes. They confirmed that in animal models of cholestatic, toxic and fatty liver disease, pericytes are the main source of collagen [181]. Additionally, a recent study reported that αv integrin depletion in liver pericytes protected mice from liver fibrosis [182]. Whether a specific pericyte subpopulation is responsible for hepatic fibrous tissue formation remains unknown.

In skeletal muscle, PDGFRβ^+/NG2$^+$ pericytes participate in the formation of a fibrotic scar after acute injury as shown by fate-mapping using an inducible tetracycline transactivator-based system [121]. Recently, we showed that skeletal muscle type 1, but not type 2, pericytes are fibrogenic when exposed to transforming growth factor β (TGFβ) in culture, and *in vivo*, only type 1 produce collagen, which increases fibrous tissue deposition in the skeletal muscle of old mice.

Although pericytes have been associated with regeneration, blocking the whole population would prevent tissue repair after injury. We must quantify the endogenous pericyte contribution to fibrous tissue formation relative to other fibrogenic cells (e.g., tissue resident fibroblasts) in skeletal muscle with aging. Recombination-based lineage tracing and ablation of type 1 pericytes may help to find the answer, but so far the only marker we found differentially expressed in pericyte subpopulations is nestin–GFP. Tracking pericyte fate or ablating a subtype *in vivo* will require the discovery of markers that are expressed in only one subtype, perhaps using single-cell microarrays to characterize their specific expression

profiles. Future studies might target type 1 pericytes to reduce skeletal muscle fibrosis in old mammals.

In contrast with the dominant role of pericytes in liver and skeletal muscle fibrosis, their contribution in kidney, lung and spinal cord remains controversial [57,70,183-186]. In the kidney, their role is under active investigation and debate. Fibrogenic cells were reported to expand from a perivascular location in an accelerated model of angiotensin II-induced renal fibrosis approximately a decade ago [187]. A previous study reported that pericytes and perivascular fibroblasts in the kidney expand after induction of renal fibrosis using type 1 collagen–FP mice [188]. The group concluded that the major source of fibrogenic cells are interstitial pericytes [184] using a Cre− reporter strategy to label renal epithelial cells or pericytes in mice subjected to unilateral ureteral obstruction and ischemia-reperfusion injury models.

In sharp contrast, another group reported that pericytes do not participate in kidney fibrosis. The authors created a mouse in which the pericyte-marker promoter controlled thymidine kinase expression to ablate pericytes in response to ganciclovir administration. Following unilateral ureteral obstruction, the grade of fibrosis did not change, suggesting that pericytes do not form renal fibrous tissue [183]. In agreement with this report, we found that only type 1 pericytes accumulate in the kidney fibrotic area after unilateral ureteral obstruction, but they do not produce collagen (A. Birbrair, T. Zhang, D. C. Files, S. Mannava, T. Smith, Z. M. Wang, M. L. Messi, A. Mintz and O. Delbono, unpublished work). Cell depletion, mouse strain, genetic tagging and model-specific differences may explain some discrepant conclusions about the role of pericytes in kidney fibrosis.

In the lungs, pericytes expressing NG2 and PDGFRβ proliferate after bleomycin-induced fibrosis [186]. That study suggests that pericytes should be excluded as the origin of fibrogenic cells [186], but a recent fate-mapping report showed that FoxD1$^+$ pericytes contribute to pulmonary fibrogenesis [185]. This apparent discrepancy could be explained by the first study's use of inducible NG2−CreER transgenic mice. The recombination efficiency was low, and thus the analyses did not include the whole pericyte population. In a small percentage, we found that type 1, but not type 2, pericytes contribute to collagen production in the lungs (A. Birbrair, T. Zhang, D. C. Files, S. Mannava, T. Smith, Z. M. Wang, M. L. Messi, A. Mintz and O. Delbono, unpublished work).

In the spinal cord, pericytes expressing Glast were previously found to participate in the formation of scar tissue after injury. The authors performed contusive injury in tamoxifen-inducible Glast−CreER mice. Following the dorsal funiculus incision, the number of Glast$^+$ pericytes increased and formed the core of the scar [70]. However, whether the cells identified as pericytes are a subset of glial cells and directly responsible for fibrosis is unknown [189-191]. The use of a NG2/collagen-specific transgenic reporter mouse may clarify this ambiguity. Soderblom et al. [57] determined that, unlike perivascular fibroblasts, NG2$^+$ pericytes are not major collagen-producing cells after contusive spinal cord injury. We found that type 1, but not type 2, pericytes increase and accumulate at the injured site 2 weeks after spinal cord and brain contusion. Type 1 pericytes differ from collagen-producing PDGFRβ^+ cells in the injured cortex (A. Birbrair, T. Zhang, D. C. Files, S.

Mannava, T. Smith, Z. M. Wang, M. L. Messi, A. Mintz and O. Delbono, unpublished work), suggesting that their role in tissue repair after CNS injury differs [57,70].

In the heart, pericytes are the second largest cellular population [192]. Experimentally, their exact pathogenic role in myocardial fibrosis is unknown, but a review article suggests that it may be significant [193]. We discovered that type 1 pericytes are recruited and accumulated in the interstitial space surrounding fibrotic tissue in the ischaemic zone but do not contribute to tissue fibrosis (A. Birbrair, T. Zhang, D. C. Files, S. Mannava, T. Smith, Z. M. Wang, M. L. Messi, A. Mintz and O. Delbono, unpublished work). Whether proliferation and migration of type 1 pericytes are important in the pathogenesis of heart fibrosis has not been studied.

Similar studies investigating the relationship between pericyte subtypes and cancer-activated fibroblasts in the tumour microenvironment are needed. To what extent pericytes contribute to tissue fibrosis, especially in humans, remains an open question. All the present studies were conducted in animal models. If we can unravel pericyte subpopulation mechanisms in human tissues, we may be able to design organ-specific antifibrotic therapies.

PERICYTES AND ANGIOGENESIS

Pericytes play a leading role in angiogenesis [194], promoting endothelial cell survival and migration [68,195-198]. Without them, capillaries rupture at late gestation [14], and nascent vessels regress [199]. In adults, most vessels are quiescent; nevertheless, pericytes participate in angiogenesis during wound healing [200] and tumour growth [201]. For this reason, they have been proposed as targets for pharmacological therapy, and since they are heteregoneous, and subsets have different functions, targeting only the subpopulation involved in angiogenesis may be more efficient.

We examined whether pericyte subtypes participate equally in angiogenesis. We found that type 2 pericytes are angiogenic *in vivo* and retain that potential *in vitro*. Only type 2 pericytes are recruited during tumour vessel formation [202]. Thus, they are the better cellular target for therapeutically inhibiting angiogenesis in cancer. Because of their angiogenic capacity, pericytes can be used to ameliorate limb ischaemia after transplantation into a mouse model of critical hindlimb ischaemia [123]. Again, we showed that type 2 pericytes improve blood flow in mice subjected to femoral artery ligation [202]. These results indicate that type 2 pericytes show promise for vascular therapy in ischaemic illnesses.

Future work should investigate the mechanisms underlying type 2 pericytes' angiogenic potential and whether their ablation affects normal vascular function. To apply their beneficial effects on angiogenesis to human therapy, the complete type 2 pericyte transcriptome should be explored for a specific marker to identify them in wild-type species. Currently, they can only be identified in the nestin–GFP transgenic mouse [73,203,204].

PERICYTES AND AGE-DEPENDENT DECLINE IN TISSUE REPAIR

The mechanisms that impede tissue repair, particularly skeletal muscle regeneration with aging, remain poorly understood [62,205-207]. Some studies suggest that the decrease in, and reduced function of, stem cells play an essential role [208-211]. Previously, significant changes to the skeletal muscle pericyte microenvironment with aging have been reported [212]. Furthermore, some pericytes may not express a specific receptor that mediates the signalling pathway required for their differentiation, resulting in the emergence of a subpopulation with poor sensitivity to a specific agonist. Reduced expression of the Notch ligand Delta affects Notch signalling and consequently impairs muscle regeneration [207]. The TGFβ, Wnt and insulin-like growth factor (IGF) pathways have also been associated with age-dependent impairment of muscle regeneration [213-216].

Because fibrous tissue accumulates in the skeletal muscle with aging [217-223], TGFβ, a profibrotic cytokine [224], must be examined. The constitutively active PDGFRα-knockin mouse exhibits fibrosis both systemically and in the skeletal muscle [225]. It can be used to determine whether impaired PDGFR signalling with age affects different pericyte subtypes [226] and how extrinsic and intrinsic pericyte factors contribute to impaired muscle regeneration. Cell-intrinsic changes may be reversible or not but, either way, represent another source of heterogeneity. One pericyte subtype may be more prone to senescence or apoptosis with aging than another, with consequent imbalance in their relative proportions, and the aged environment may select for a subtype with distinct regenerative potential [227]. The newly characterized pericyte subtypes prompt investigation of reported heterogenous stem cells [228-231] and their role in tissue regeneration.

Future studies should: (i) evaluate whether the described roles of pericytes in several tissues change in the aging environment; (ii) identify whether pericyte subpopulations are affected differently by age; (iii) determine pericyte fate when exposed to such ligands as TGFβ, IGF-I, PDGF-AA, Wnt and Delta; (iv) test pericytes' differentiation potential (myogenic, fibrogenic or adipogenic) when incubated with PDGFRα-, TGFβ receptor (TGFβR)-, IGF-I receptor (IGFR)-, Frizzled- or Notch Fc-chimaeric receptors, which compete for ligands with pericyte receptors *in vitro*; and (v) induce muscle regeneration by activating any of the pathways involved in pericyte subtype signalling by injecting or locally overexpressing the ligand or receptor, respectively.

CONCLUDING REMARKS

Recent studies support unique functions for pericyte subsets that may enable new therapeutic strategies. Although overall, pericytes are multipotent stem cells, their subpopulations are differentially committed to specific lineages (oligopotent) (Figure 1). To translate animal research on pericyte subtypes to humans, specific markers for pericyte subpopulations must be validated in human tissues to clarify their endogenous physiological response to physiological and pathological conditions. Microarray analysis may provide new markers allowing ablation of a specific pericyte subtype *in vivo*. Whether pericyte subtypes have distinct requirements for self-renewal, activation and proliferation remains unknown,

but using them indiscriminately for tissue repair may result in excessive fibrosis, fat accumulation and, eventually, tumour expansion.

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Abbreviations

CNS	central nervous system
FSP1	fibroblast-specific protein 1
Glast	glutamate aspartate transporter
IGF	insulin-like growth factor
LEPR	leptin receptor
MSC	mesenchymal stem cell
NG2	nerve/glial antigen-2
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PPARγ	peroxisome-proliferator-activated receptor-γ
αSMA	α-smooth muscle actin
TGF	transforming growth factor

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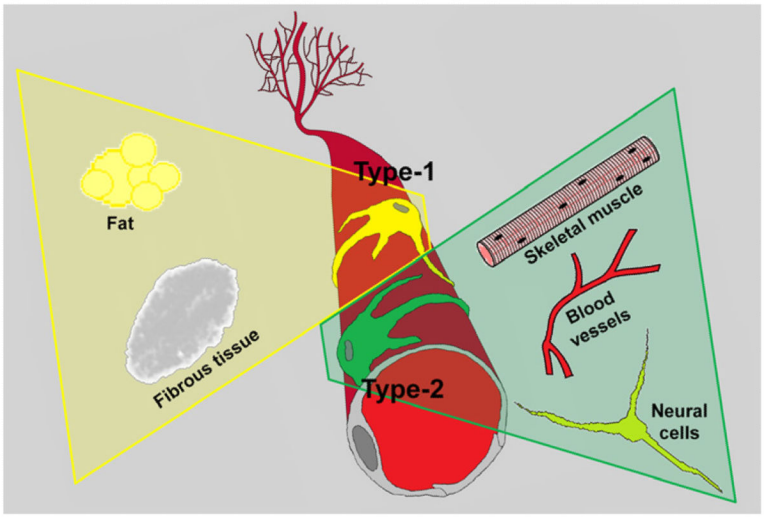

Figure 1. Hypothetical diagram of the roles of pericyte subtypes in tissue formation

Two subpopulations of pericytes are associated with blood vessels: type 1 (yellow) and type 2 (green). Pericyte subtypes are oligopotent and their ability to differentiate is restricted.