

Chapter 2

Morphology and Properties of Pericytes

Paula Dore-Duffy and Kristen Cleary

Abstract

Pericytes were described in 1873 by the French scientist Charles-Marie Benjamin Rouget and were originally called Rouget cells. The Rouget cell was renamed some years later due to its anatomical location abluminal to the endothelial cell (EC) and luminal to parenchymal cells. In the brain, pericytes are located in precapillary arterioles, capillaries and postcapillary venules. They deposit elements of the basal lamina and are totally surrounded by this vascular component. Pericytes are important cellular constituents of the blood–brain barrier (BBB) and actively communicate with other cells of the neurovascular unit such as ECs, astrocytes, and neurons. Pericytes are local regulatory cells that are important for the maintenance of homeostasis and hemostasis, and are a source of adult pluripotent stem cells. Further understanding of the role played by this intriguing cell may lead to novel targeted therapies for neurovascular diseases.

Key words: Angiogenesis, Blood–brain barrier, Capillaries, Contractility, DNA repair, Endothelial cells, Gap junction, Homeostasis, Migration, Neurovascular unit, Pericyte, Stem cells, Stress response, Vascular injury

1. Introduction

Pericytes were described in the late 1800s by the French scientist Charles-Marie Benjamin Rouget (1) and were referred to as the Rouget cell. It was not until the early 1900s that Rouget’s work was confirmed as reviewed by Doré (2) and the Rouget cell was renamed as the pericyte. Since its discovery there has been considerable confusion and controversy reflected in the numerous conflicting definitions of the pericyte found in the literature. The pericyte has been referred to as: (a) A contractile, motile cell that surrounds the capillary in a tunic-like fashion (1). (b) A branching contractile cell on the external wall of a capillary and peculiar elongated, contractile cell wrapped around precapillary arterioles “outside” the basement membrane (3). (c) A slender, relatively undifferentiated connective tissue cell in the capillaries or other

small blood vessels also called the adventitial cell (4). (d) A smooth muscle/pericyte or smooth muscle cell of the capillaries (5, 6). A broad flat cell with slender projections that wrap around the capillaries (6). (e) A stem or mesenchymal-like cell, associated with the walls of small blood vessels. As a relatively undifferentiated cell, it serves to support these vessels, but it can differentiate into a fibroblast, smooth muscle cell, or macrophage as well if required (6–14).

Despite nearly 130 years of investigation, the role of the pericyte is still somewhat of a mystery. This is due, in part, to the relatively low numbers of pericytes in most tissues. The ratio of pericytes to EC varies from species to species and organ to organ and varies even within the capillary bed. In the brain the average ratio of pericytes to EC in the rat capillary is 1:5. In the mouse the ratio is 1:4 and in humans 1:3–4. This low number is further augmented by the difficulty of isolating pure primary pericytes (15). Once isolated, pericytes rapidly differentiate along multiple lineages depending on the regulatory signals present in the microenvironment. It is this pluripotentiality and the ability to migrate as well as the lack of a pericyte specific marker that has lead to the enormous confusion about this cell (14). In this chapter, the role of the pericyte as an adaptive regulatory cell of the neurovascular unit that is important in the maintenance of tissue homeostasis will be discussed, as well as the role of the pericytes as a source of adult stem cells and the potential role of pericytes in development of disease pathology.

2. Morphology

2.1. Central Nervous System (CNS) Pericyte Morphology

In the mature CNS capillary, the pericyte is located between the EC and parenchymal astrocytes and neurons (Fig. 1). Pericytes have a prominent round nucleus that clearly differs from the elongated cigar shaped nucleus of the EC. The pericyte extends long

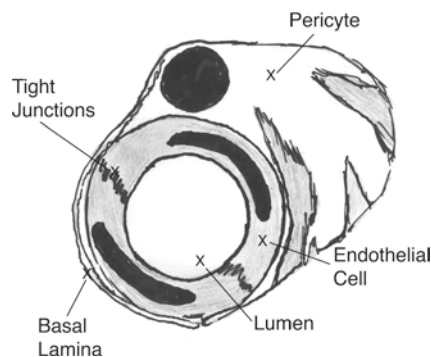


Fig. 1. Cross section of a CNS capillary is shown in cartoon form. The pericyte is located between the endothelial cells (EC) and astrocytes (not shown). Pericyte projections (*white*) wrap around the capillary (*gray*). The pericyte is totally surrounded by basal lamina.

processes that extend over the vessel wall. The morphological pattern of projections appears to be somewhat heterogeneous (Fig. 2). Pericyte projections can extend around the capillary (Fig. 2a–c) as originally described by Rouget (1). The classic wrapping pattern is also somewhat heterogeneous. The most common association of the pericyte with the capillary is one in which the pericyte processes are broad and span a large somewhat continuous surface of the vessel (Fig. 2a, d). Alternatively these

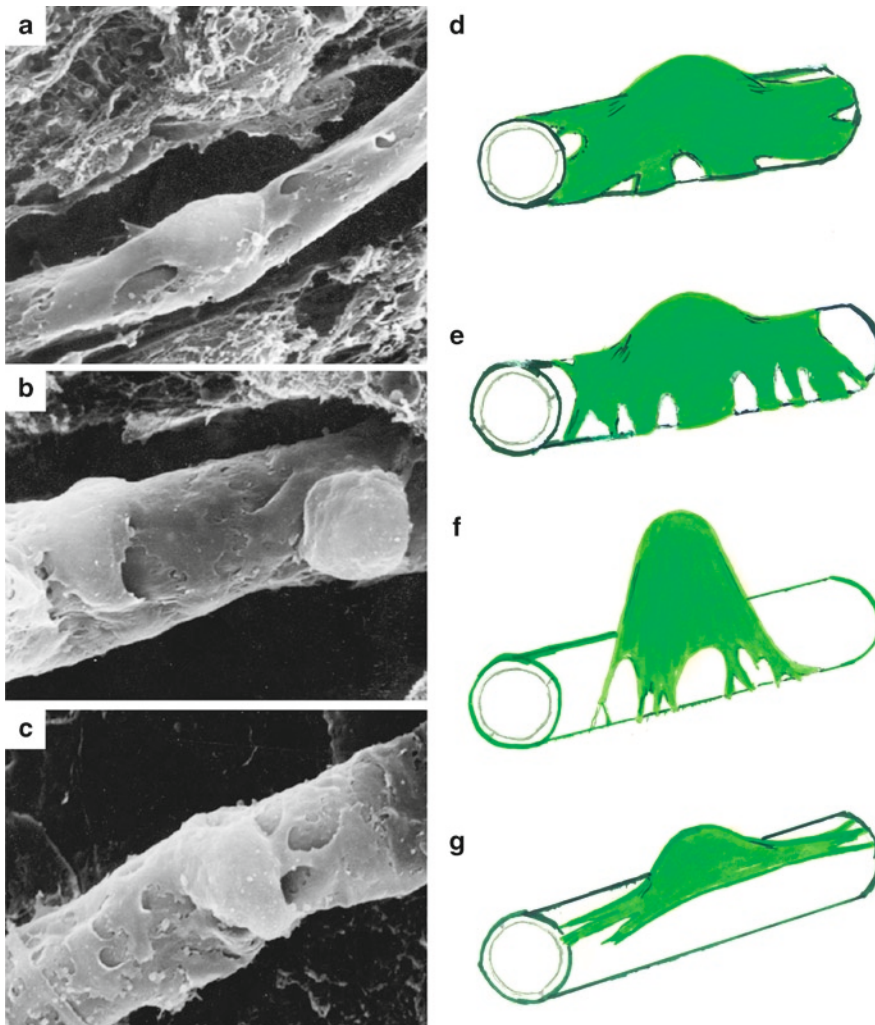


Fig. 2. Three scanning electron micrographs of segments of rat CNS capillaries are shown (a–c) along with four cartoons depicting the structural association of pericytes with microvessels (d–g). The common pattern is the pericyte encircling the capillary with broad, virtually continuous projections that cover a large surface area of the microvessel (a, d). The second pattern shows pericytes wrapping around the capillary, but the area is more defined and smaller and the pericyte projections are finger-like in shape (b, c, e). The third pattern is that of migrating pericytes (b, f). This pattern is predominantly seen following injury and during the early stages of angiogenesis. The fourth pattern shows that the pericyte is positioned longitudinally in a polar fashion along the microvessel (g). This pattern may reflect pericytes migrating along the vessel or may reflect transition pericytes. This pattern is seen at arteriolar/capillary junctions and during angiogenesis.

processes may form finger-like projections that are more confined and surround a more finite portion of vessels (Fig. 2b, c, e). A third pattern of pericyte orientation in the microvessel involves a retraction of projections and this represents a migrating pericyte (Fig. 2b, f) (16). Pericytes may also extend along the long axis of the capillary which represents longitudinal migration (Fig. 2g). This pattern is more commonly seen during angiogenesis. In normal capillaries, the wrapping pattern predominates but under pathological conditions the migrating pattern increases. It is likely that these patterns represent functional differentiation of pericytes rather than heterologous subsets.

The CNS pericyte is surrounded by the basal lamina on all sides. During development and during angiogenesis the pericyte deposits basal lamina components (14). Even pericyte projections, observed using electron microscopy, have a thin layer of basal lamina. The basal lamina has been shown to thicken or thin in response to stress stimuli (17–20). Changes in the basal lamina can be directly associated with pericyte expression of proteases (16) and ultimate migration from its vascular location (17, 21).

The intact basal lamina may not only provide anchoring and structural integrity to the capillary but it may also be involved in regulation of pericyte function and differentiation. It seems intuitive that there must be a reason why the pericyte is surrounded by laminal proteins. $\text{Av}\beta 8$ integrin is important in neurovascular cell adhesion (22, 23). Pericytes encased in the basal lamina or exposed to laminal proteins do not usually differentiate (*Dore-Duffy, unpublished observations*). Thus migration through the basal lamina is necessary before cells can function in their stem cell capacity. Regulation at the level of the basal lamina may also be integral to vascular adaptability to an ever-changing environment and to pericyte signaling mechanisms (24).

Within its capillary location, the pericyte may signal nearby EC (25), astrocytes (26), neurons, smooth muscle cells, and perhaps other pericytes (14). Pericyte-EC contacts include peg and socket arrangements (27, 28) and gap junctions (29, 30). Gap junctions allow pericytes to communicate through the exchange of ions and small molecules. Peg-and-socket contacts enable pericytes to penetrate through the basal lamina and make contact with other cells and nearby vessels (27, 28). Junctional complexes including adhesion plaques also support transmission of contractile forces from pericytes to other cells. Pericyte gap junctions contain N-cadherin, a variety of adhesion molecules, β -catenin, extracellular matrix (ECM) molecules such as fibronectin, and a number of integrins (30, 31). Thus, pericytes are involved in highly complex signaling cascades that enable this cell to respond to changes in the microenvironment. However, it is unclear whether gap junctions and peg and socket contacts are naturally present or whether they are initiated during changes in functional activity.

For example, it is known that pericytes interdigitate with ECs during the early phases of angiogenesis and with neurons during the maturation of newly formed vessels (32). These sites of communication are altered under pathological conditions. During cerebral edema or diabetes, gap junctions are substantially decreased or disrupted in retinal pericytes (33–35). Diabetes-induced changes in gap junctions may be regulated by high glucose (36). Pericyte-EC communication via gap junctions is fundamental to the adaptive responses to compromised bioenergetic homeostasis (37). Crosstalk between ECs, pericytes, as well as astrocytes is involved in regulation of insulin transport (26). Pericyte/endothelial cross talk is also integral to physiological angiogenesis (38), and is likely to be important in adaptation to hypoxic injury and focal capillary contractility.

2.2. Pericyte Markers

Identification of the pericyte in culture or in situ is difficult. They can be definitively identified at the electron microscopic (EM) level or in semithin sections where their location relative to the basal lamina can be seen (Fig. 1). EM morphology is detailed and discussed in a number of excellent articles (21, 39–41). Pericytes can also be identified in capillary isolates by the shape of their nucleus which is round while the EC nucleus is elongated and cigar-shaped and can be easily delineated using a nuclear dye (14). Many investigators have used antibody directed against alpha smooth muscle actin (α SMA) to identify pericytes (Table 1). While pericytes are capable of expressing α SMA, the expression of this protein in vivo may be associated with functional heterogeneity within the capillary and in vitro may be a marker of dedifferentiation. In their capillary location, most pericytes are α SMA negative (8, 14, 42, 43). In brain, only those pericytes that are located near arterioles are routinely immunoreactive for α SMA (14). Expression of this protein can be induced within the capillary and may be related to the role of the pericyte in focal regulation of capillary blood flow (44–47) and in the acute stress response (14). In primary cultures, less than 5% of freshly isolated capillary pericytes express α SMA (8, 43) but nearly 100% express this marker by day 7 (Fig. 3) (48).

Bovine retinal pericytes express potassium (K^+) channels (49). In vasa recta pericytes, elevation of extracellular K^+ hyperpolarizes pericytes and this is reversed by barium (Ba^{2+}), confirming the presence of strong inward rectifier K^+ channels (Kir) (50). Kir, however, is also strongly expressed in EC and arteriolar smooth muscle cells (51). Transcription profiling of pericyte-deficient brain microvessels isolated from platelet-derived growth factor beta ($PDGF\beta$) $-/-$ and $PDGF\beta$ receptor ($PDGF\beta R$) $-/-$ mouse mutants has identified new candidates for pericyte markers. The ATP-sensitive potassium-channel Kir6.1 (also known as *Kcnj8*) and sulfonylurea receptor 2, (*SUR2*, also known as *Abcc9*), as well as delta homologue 1 (*DLK1*), have been proposed as specific markers for brain pericytes. The three

Table 1
This table outlines pericyte markers

Pericyte marker	Reference
3G5-defined ganglioside	(62)
140 kDa Aminopeptidase N	(60)
Angiopoietin 1	(61)
DLK1	(52)
ICAM-1	(42)
Kcnj8	(52)
K ⁺ channels/Kir	(49–51)
Nestin	(9)
NG2	(8, 9, 53, 59)
OX-42/ α M	(54)
PDGF α R	(14)
PDGF β R	(8, 14, 43, 58)
RGS-5	(55)
α SMA	(8, 14, 42, 43, 145, 146)
SUR2/Abcc9	(52)
VCAM-1	(42, 147)
Vimentin	(8, 13, 56, 148)

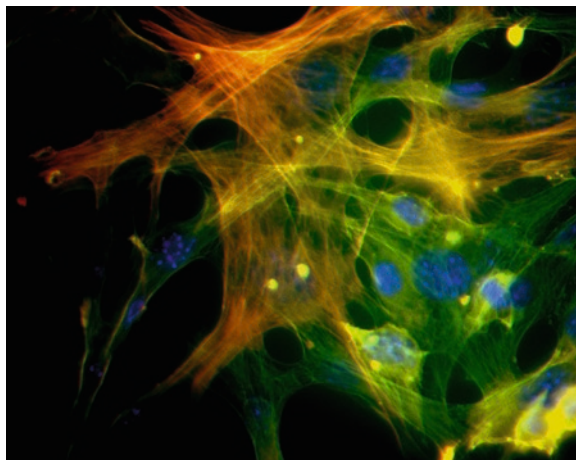


Fig. 3. Primary rat pericytes (4 days old) grown in DMEM plus 20% fetal calf serum. Cells were fixed in 4 % glutaraldehyde, permeabilized with Triton X-100 and dual stained for expression of beta actin (*green*) and alpha smooth muscle actin (*red*). In this culture 30% of the cells expressed the smooth muscle phenotype. One hundred percent of the cells expressed the receptor for platelet derived growth factor beta (not shown).

proposed brain pericyte markers are signaling molecules implicated in ion transport and intercellular signaling (52). The selectivity of expression has yet to be confirmed and it is possible that these markers are not expressed in adult pericytes.

Pericytes are positive for the chondroitin sulfate proteoglycan NG2, formerly known as the high molecular weight melanoma associated antigen (53) and nestin (9). They also express vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (42). We have reported that pericytes express the OX-42 marker (α M) in vivo and in isolated capillaries (54). However, in primary culture, this marker associates at focal adhesion sites and is down-regulated with time. The adult CNS pericyte expresses a number of proteins that are useful in their identification (8, 48, 55). They express vimentin but not desmin (8, 56). Developmental markers such as the regulator of G-protein signaling (RGS-5) protein have been identified in knockout mice (57). This protein is expressed during embryonic development and lost after birth. In our hands it is not expressed in normal adult CNS pericytes (*Dore-Duffy unpublished observations*). However, expression of RGS5 has been reported in tumor pericytes during angiogenesis (55). Adult pericytes express PDGF β , PDGF β R (58), and NG2 chondroitin sulfate proteoglycan (8, 53, 59). Pericytes are also known to express PDGF α R (14) but we have not yet tested this in brain sections. Other markers expressed by pericytes include the 140 kDa aminopeptidase N (60), angiopoietin 1 (61), and a 3G5-defined ganglioside (62). The ganglioside 3G5 is not expressed by all pericytes (63) and is expressed by a large number of other cells including islet cells, follicular cells, melanocytes, and pancreatic and adrenal cells.

The lack of a definitive pan-marker for pericytes may be due to the fact that these cells are multipotent self-renewing cells (9, 14). This will be discussed in more detail under [Subheading 3](#). When pericytes are subcultured from freshly isolated capillaries they undergo a period of quiescence that is followed by development of the α SMA phenotype. This may reflect either dedifferentiation, if one assumes that pericytes are derived from mesenchymal cells, or may reflect differentiation of a quiescent stem cell along the mesenchymal lineage (64). Thus α SMA cannot be used to definitively identify pericytes nor can the lack of expression be used to exclude pericytes.

3. Properties

3.1. Pericytes and the Blood–Brain Barrier (BBB)

The BBB regulates the passage of various nutrients and essential components, proteins, chemical substances, and microscopic organisms between the bloodstream and the parenchymal tissue.

The anatomical constituents of the BBB are the EC, pericytes, and basal lamina (matrix proteins) that together with the astrocytes, neurons, and possibly other glial cells comprise the neurovascular unit. Coordinated cell-to-cell interactions between cells of the neurovascular unit regulate a wide variety of functions that include development, BBB permeability, cerebral blood flow, and the stress response.

Dysregulation at the neurovascular level is linked to many common human CNS pathologies, making the neurovascular unit a potential target for therapeutic intervention. Together the cells of the neurovascular unit adapt to environmental changes and make fine-tuned regulatory decisions that maintain homeostasis and promote tissue survival. Nowhere is such tight regulation more important than in the brain where bioenergetic and metabolic homeostasis is integral for neuronal survival. The role of the CNS pericyte in the neurovascular unit is still largely unknown. Pericytes were once thought to function as a support or scaffolding structure. It is known that pericytes are highly complex regulatory cells that communicate with ECs and other cells of the neurovascular unit such as neurons and astrocytes by direct physical contact and through autocrine and paracrine signaling pathways (8, 11–13, 27, 65). It seems intuitive that loss or dysfunction of the pericyte or of any of the cells comprising the neurovascular unit has highly deleterious effects.

3.2. Contractility

The concept that pericytes regulate blood flow at the capillary level was originally proposed by Steinach and Kahn in 1903 (45) and Ni in 1922 (66). Both scientific groups studied the effects of toxic and electrical stimulation on capillary diameter. Doré reviewed this area in 1923 (2). The concepts put forward in this review are on target with what is known today. As stated by

Doré, (2): *Until a few years ago the capillaries were regarded as elastic tubes undergoing passive distension in accordance with the general blood pressure, the state of contraction or dilatation of the supplying arterioles, and the nutrition of the vascular walls. There is now, however, conclusive evidence that the capillaries play an independent part in the peripheral circulation, that they possess the intrinsic property of contraction and relaxation, and are under the direct influence of the nervous system.*

Pericytes have receptors for a large number of vasoactive signaling molecules (8, 14) suggesting that they have the capacity to be involved in cerebrovascular autoregulation. Nonneural pericyte expression of α SMA and desmin, two proteins found in smooth muscle cells, as well as their adherence to the endovascular cells make them potential candidates in regulation of capillary diameter and focal capillary blood flow (8, 27, 67–70). Electrical stimulation of retinal and cerebellar pericytes is reported to evoke a localized capillary constriction (47). ATP in the retina or

noradrenaline in the cerebellum also results in constriction of capillaries by pericytes. Glutamate reverses the constriction produced by noradrenaline. Following simulated ischemia and traumatic brain injury (TBI), capillary pericytes are induced to express α SMA. Thus, it is likely that pericytes modulate blood flow in response to acute changes in neural activity and/or metabolic need. For example, other investigators have shown that capillary contraction can be directly linked to metabolic need (69, 71). Exposure to lactate increases pericyte calcium, contraction, and capillary lumina become constricted. The contractile response appears to involve a cascade of events resulting in the inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchangers on the EC (71). Hypoxia, which closes gap junctions, switches the effect of lactate from contraction to relaxation. This further suggests that when energy supplies are ample, lactate may stimulate vasoconstriction, and under hypoxic conditions, induce vasodilation. Thus, pericyte function may be linked with local vascular adaptation to changes in local bioenergetic requirements.

3.3. Pericytes Are Multipotential Stem Cells in the Adult Brain

Adaptations to stress at the vascular level include functional and phenotypic changes involving differentiation along mesenchymal and neural lineages, and lend credence to the idea that pericytes are multipotential stem cells in the adult brain and in other tissues. That pericytes are stem cells is supported by a host of information from historical work and from more recent literature. We will speculate on the importance of pericyte stem cell activity in survival and DNA repair and how dysregulation of pericyte function may lead to disease.

The pluripotentiality of pericytes has been proposed for many years and has been reviewed (8, 10–12, 14, 65). As early as 1970, it was proposed that there is a similarity between neuroglial cells and pericytes (72). Katenkamp and Stiller (73) proposed that myofibroblasts were derived from pericytes and pericytes were multipotent stem cells. They further proposed that these cells are not only functional in dermatofibroma but are integral to connective tissue regeneration (74) and involved in interferon gamma ($\text{IFN-}\gamma$) (75) release. Nestin is induced in liver stellate cells during transition from the quiescent to the activated phenotype in culture (76). These cells also express glial fibrillary acidic protein (GFAP) and neural cell adhesion molecule (NCAM). They proposed a potential embryonic origin of these cells. In the adult liver, the replicating cells including endothelial, Kupffer, stellate cells (Ito or pericytes), bile duct epithelium, and granular lymphocytes (pit cells), were found to be stem cells (77). The ability of pericytes to form bone nodules in vitro (78) provided the basis for a number of elegant studies predominantly by Anne Canfield's laboratory showing that pericytes are a source of osteogenic progenitor cells (79–83). Pericytes have also been shown to produce

chondrocytes and adipocytes (84). As early as 1993, it was shown that bone marrow stromal cells are mesenchymal, express vimentin, and can be induced to express α SMA in culture (85). These cells are multipotent and share many pericyte characteristics. An alternative hypothesis is that these cells are derived from a common precursor. Multipotent stem cells isolated from human reaming debris collected during surgical treatment of long bone diaphyseal fractures differentiate along the osteogenic pathway and can be redirected to a neuronal phenotype (86). These cells also resemble pericytes. It has been reported that growth factors such as bovine fibroblast growth factor (bFGF) and epidermal growth factor (EGF) stimulate pericyte proliferation and angiogenesis (87). Both EGF and bFGF responsive vascular stem cells have been reported in the rat and avian microvasculature (88–90). Additional reports suggest that pericytes differentiate into fibroblasts (17, 83, 91), endothelial cells (90), adipocytes (92), chondrocytes (82), and macrophages/dendritic cells (54, 93).

We have investigated the neural potential of primary pericytes subcultured from isolated rat CNS capillaries (9). Using fluorescence-activated cell sorting (FACs) analysis, our study demonstrates that adult CNS capillaries contain NG2 and nestin-positive pericytes, markers not expressed in EC populations. Pericyte BRDU/nestin-positive, bFGF-induced spheres ultimately differentiate and are composed of cells of neural cell lineage. Pericytes undergo self-renewal and increase in number after subculturing. By clonal analysis, multipotent pericytes differentiate along multiple lineages that include astrocytes, neurons, oligodendrocytes, and α SMA-positive cells that are NG2/nestin-positive and resemble primary pericytes. There is no evidence of cell fusion in these studies. When spheres are disrupted, cells coexpressing oligodendrocyte and astrocyte markers are noted. Pericytes also generate neurospheres directly from cultured rat capillaries at a faster rate than seen with primary pericytes (14) suggesting that ECs can enhance this process. ECs secrete a substance that enhances neurosphere formation (94) while smooth muscle cells do not enhance neurosphere formation. While capillary pericytes are a source of adult stem cells, ECs within the vascular niche provide trophic support.

Subsequent studies have confirmed these findings and identified pericytes from other organs as adult stem cells. Liver pericytes (Ito cells, stellate cells) are liver cell progenitors (95, 96). Skin pericytes are the source of regenerating skin tissue in adults (97). Rajkumar et al. (98) examined mechanisms by which microvascular injury leads to dermal fibrosis in diffuse cutaneous systemic sclerosis. They hypothesized that microvascular pericytes or fibroblasts transdifferentiate into myofibroblasts. Purified pericytes also demonstrate high myogenic potential in culture and in vivo (99–101). Cells of testicular blood vessels (vascular smooth muscle

cells or pericytes) are the progenitors of Leydig cells (102). Resembling stem cells of the nervous system, the Leydig cell progenitors are characterized by the expression of nestin. The pulp of human teeth contains a population of cells with stem cell properties and it has been suggested that these cells originate from pericytes (103). Pulp stem cells express molecules of the Notch signaling pathway (Notch3). Notch3 was coexpressed with RGS5. RGS5 induction may be coregulated with stem cell activity. Thus, in six separate tissues namely, teeth, brain, skin, muscle, prostate and liver, pericytes are a source of tissue progenitor cells in adult tissue.

The pericyte has a very broad stem cell potential that goes beyond organ specific production of progenitor cells. In serum-containing culture medium, primary CNS pericytes (2–4 days old) take on a macrophage/dendritic cell-like phenotype (14, 54, 93). During this period, pericytes express macrophage markers and can present antigen (54). Upon exposure to interferon, pericytes express MHC class II antigen and can present antigen to sensitized splenic T-cells (93). Pericytes continue to differentiate becoming 100% α SMA positive on days 7–10 and express other markers such as the integrin β 1 characteristic of mesenchymal stem cells (MSC). With prolonged culture, pericytes form nodules that produce mineralized bone by 21 days in culture (14, 81). These nodules are alizarin red positive. In the same culture, there are other cell types known to be derived from mesenchymal lineage. Thus, in vitro data supports the concept that with the correct environmental cues CNS pericytes may form MSC and then differentiate to bone, adipocytes, smooth muscle cells, and endothelial cells. With different cues, pericytes differentiate along the neural lineage.

In the adult, proliferating stem cell activity is usually found in a perivascular location in response to stress or injury (104, 105). However, the exact mechanism that regulates induction, proliferation then reprogramming, and differentiation of adult stem cells is not known. Pericytes migrate from their vascular location in response to stress injury (21) and remain in a perivascular location where they may encounter local signaling molecules that dictate their subsequent activities such as migration, proliferation or differentiation. It is likely that they may also migrate back to the vascular location. Perivascular pericytes proliferate during the developmental angiogenic response (106) and during physiological angiogenesis (48). Pericyte signaling molecules that are involved in regulation of angiogenesis are also involved in neurogenesis (107, 108). Pericytes synthesize the proangiogenic cytokine, vascular endothelial growth factor (VEGF) (109). VEGF augments pericyte proliferation in an autocrine fashion (109), promotes differentiation of multipotent chondrocytic stem cells (110), and promotes migration and vascular instability (111). Pericytes are also responsive to growth factors and other signaling

molecules important in regulation of neurogenesis (8, 109, 112). Thus, it is possible that the response to injury and stress at the tissue level is coregulated with stem cell differentiation in the adult.

4. Pericytes and Disease

As discussed above, pericytes play an important role in the maintenance of vascular and tissue homeostasis and are integral to injury responses. Under normal conditions the pericyte is relatively quiescent and is essential for vascular stability. Under conditions of stress or injury, the pericyte undergoes phenotypic and functional changes that may include migration, proliferation or differentiation. How these events that include pericyte reprogramming are coordinated at the molecular level needs to be determined. However, it is clear that pericyte dysfunction or the loss of pericytes is likely to play an important role in the pathogenesis of disease.

Pericyte loss or a reduced pericyte to EC ratio may be achieved through migration of pericytes from their microvascular location under pathological or physiological conditions, selective pericyte death or from reduced pericyte turnover or maintenance. Pericytes migrate naturally during the early phases of physiological angiogenesis to make way for growing sprouts (113, 114), or in response to stress or injury (21). Migration following TBI is thought to promote survival as pericytes remaining in their vascular location show signs of degenerative activity (21). However, migration is also thought to play a pathogenic role in diabetic retinopathy (115). Decreased pericyte to EC ratios have been observed following TBI (21) and stroke (116), multiple sclerosis (117–121), brain tumor (122, 123), diabetic retinopathy (124), aging (125, 126), and in a variety of angiopathies (127). Pericyte loss may also play a role in Alzheimer's disease, however; enhanced pericyte coverage of some vessels may suggest that increased proliferation of pericytes is an adaptation to focal loss of bioenergetic homeostasis (121, 126, 128–130). Pericyte loss due to cellular degeneration/apoptosis has been shown in hypertrophic scars, keloids (131), early diabetic retinopathy (132, 133), cancer (134–137), hyperglycemia (138), and during development (139). Premature infants have decreased pericyte coverage (140). Increased pericyte coverage may also be an indicator of vascular dysfunction. Pericyte proliferation has been associated with development of muscularization during pulmonary hypertension and is thought to be due to platelet activating factor (141).

On a more subtle level, loss of pericyte stem cell activity may also lead to disease. Stem cells must maintain a functional genome. Under continuous exogenous and endogenous stress, uncontrolled self-renewal cells can accumulate DNA errors, drive proliferative expansion, and ultimately transform into cancer stem cells. Tumor stem cells are thought to be involved in hematological malignancies, such as hemangiomas and pericytomas, as well as in solid tumors. The complex cellular mechanisms including cell cycle arrest, transcription induction and DNA repair are activated but may be dysregulated with an absence of repair machinery. Mismatch repair gene defects have been recently identified in hematopoietic malignancies, leukemia, and lymphoma cell lines (142, 143). Pericyte differentiation within the vascular wall may be considered dysfunctional. For example, differentiation along the mesenchymal lineage with bone formation may result in microcalcifications within small vessels (144) or even fatty deposition in the vascular walls. With continued knowledge of pericyte biology, it is likely that their role in disease pathology may expand.

5. Conclusion

After its identification by Rouget in the late 1800s, relatively little was published about the pericyte until 1902 when the presence of this intriguing cell was confirmed. The development of tissue culture techniques has generated considerable interest in pericyte biology. The ability to isolate pure primary pericytes has enabled scientists to study these cells *in vitro*. The development of sophisticated molecular biological techniques has enabled us to begin to clearly delineate the complex mechanisms by which pericytes communicate with other cells of the neurovascular unit. A better understanding of the mechanisms by which pericytes communicate with other cells and how altered communication may result in disease pathology is likely to yield exciting new insights as well as help in the development of a new therapeutic target in CNS disorders.

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