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REVIEW ARTICLE

From pericytes to perivascular tumours: correlation between pathology, stem cell biology, and tissue engineering

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Abstract
Purpose Pericytes were once thought only to aid in angiogenesis and blood pressure control. Gradually, the known functions of pericytes and other perivascular stem cells (PSC) have broadly increased. The following review article will summarize the known functions and importance of pericytes across disciplines of pathology, stem cell biology, and tissue engineering.
Methods A literature review was performed for studies examining the importance of pericytes in pathology, stem cell biology, and tissue engineering.
Results The importance of pericytes most prominently includes the identification of the perivascular identity of mesenchymal stem cells (or MSC). Now, pericytes and other PSC are known to display surface markers and multilineage differentiation potential of MSC. Accordingly, interest in the purification and use of PSC for mesenchymal tissue formation and regeneration has increased. Significant demonstration of in vivo efficacy in bone and muscle regeneration has been made in laboratory animals. Contemporaneously with the uncovering of an MSC identity for pericytes, investigators in tumour biology have found biologically relevant roles for pericytes in tumor formation, lymphovascular invasion, and perivascular tumor spread. As well, the contribution of pericytes to perivascular tumors has been examined (and debated), including glomus tumour, myopericytoma and solitary fibrous tumour/hemangiopericytoma. In addition, an expanding recognition of pericyte mimicry and perivascular tumour invasion has occurred, encompassing common malignancies of the brain and skin.
Conclusions In summary, pericytes have a wide range of roles in health and disease. Pericytes are being increasingly studied for their role in tumour formation, growth and invasion. Likewise, the application of pericytes/PSC for mesenchymal tissue engineering is an expanding field of interest.

Keywords Pericyte · Adventitial cell · Glomus tumour · Myopericytoma · Solitary fibrous tumour · hemangiopericytoma

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Introduction

Pericytes, also called mural cells, were once thought only to aid in angiogenesis and blood pressure control, owing to the observation of contractile, intracytoplasmic actin filaments. Today, the role of pericytes and other perivascular stem cells (PSC) has been widely expanded. This includes the identification of PSC as true mesenchymal stem cells, and with this an acknowledgment of the utility of PSC for mesenchymal tissue engineering. This also includes the elucidation of a pericyte-like phenotype in soft tissue/perivascular tumours, and the recent descriptions of the pericyte's role in protecting against tumour invasion and metastasis. These diverse functions of pericytes span areas of stem cell biology, pathology, tumour biology, and tissue engineering.

Pericytes as mesenchymal stem cell progenitors

The histologic origins of mesenchymal stem cells (MSC) have remained obscure. Scattered reports have described the possible multipotentiality of pericytes, including an ability to undergo osteogenic, chondrogenic, fibrogenic, and adipogenic differentiation [1–3]. However, it was not until Crisan et al. utilized a combination of immunohistochemical and flow cytometry analysis that the mesenchymal stem cell (MSC) identity of pericytes was fully appreciated [4]. Using a combination of immunohistochemical markers (including NG2, CD146, PDGFRB, and αSMA), the localization of pericytes was performed. Across diverse human organs, pericytes were ubiquitously identified around arterioles, capillaries and venules. Next, Crisan et al. found that isolated pericytes express MSC markers, including CD73, CD90 and CD105. They further identified the multilineage differentiation potential of purified pericytes, including an ability to differentiate down muscle, bone, fat and cartilage lineages. Since this time, multiple independent investigators have confirmed the pericytic/perivascular origins of MSC (see [5] for a review). In addition, several research groups have identified pericytes as native progenitor cells that are involved in endogenous tissue development and repair [6–8].

Adventitial cells: a second perivascular stem cell population

After isolation of pericytes, it became clear that the non-pericyte fraction of vascularized mesenchymal tissues also housed cells with MSC characteristics. This led to the identification of a second (non-pericyte) perivascular cells with MSC characteristics [9]. This cell (identified by expression of CD34 and negativity for CD146 and CD31) was identified in the tunica adventitia of larger arteries and veins—and thus named adventitial cells. When combined, pericytes and adventitial cells represent all cells with MSC characteristics within human white adipose tissue [9]. By flow cytometry and immunohistochemistry analysis, adventitial cells express typical MSC markers including CD44, CD90, CD105 and CD73. By clonal analysis, adventitial cells evidence a capacity for multilineage differentiation, including osteogenesis, chondrogenesis, and adipogenesis [9]. Taken together, pericytes and adventitial cells (collectively termed PSC) comprise approximately 39.6 % of lipoaspirate stromal tissues [10]. Unlike other MSC sources, PSC are prospectively identified using fluorescence activated cell sorting (rather than retrospective isolation via cell culture) [5, 10] (Figs. 1, 2, and 3). The combined use of pericytes and adventitial cells has been pursued for use in mesenchymal tissue engineering, involving both bone and muscle regeneration (see next section entitled "Perivascular stem cells for tissue engineering").

Perivascular stem cells for tissue engineering

The use of PSC for mesenchymal tissue engineering purposes is an expanding field [10–13]. James et al. first described the use of PSC for bone tissue engineering, using PSC isolated from human white adipose tissue [10]. Here, PSC were compared to an unsorted population of stromal cells from the same patient, and compared for in vivo bone formation in an intramuscular (or muscle pouch) model. Results showed that purified PSC held a bone forming advantage over their unpurified counterpart population (otherwise known as the stromal vasculsar fraction, or SVF). Further experiments confirmed that PSC were responsive to osteoinductive cytokines—such that supplementation with osteoinductive proteins improved the bone forming potential over cell-based grafts alone [12]. Improved endochondral bone formation with PSC was also accompanied by increased vasculaturization within and around the implant site. Moreover, implanted PSC were found to quickly adopt a perivascular location, in effect recapitulating their native distribution [12]. Further studies have been performed in an animal bone defect model [13]. James et al. utilized a mouse calvarial defect model to further compare the osteogenic potential of PSC to an unsorted stromal population [13]. Like prior studies examining intramuscular bone formation, PSC led to speedier and increased re-ossification of calvarial defects than their unpurified counterpart. Again, this was associated with increased vascularization of the surgical defect site. In aggregate, these studies suggest that purified PSC have a high innate osteogenic potential and suggest promise for their future use in bone tissue engineering.

The use of PSC for the engineering of other mesenchymal tissue types has been examined, including skeletal and cardiac muscle [4, 14]. For example, Crisan et al. used human pericytes to regenerate mouse skeletal muscle in vivo that had been injured by cardiotoxin injection [4]. Extraordinarily, purified pericytes produced at least as many myofibers as did purified CD56+ myoblasts in their model system. Similar results were found by independent investigators, confirming the myogenic potential of PSC [8]. Recent evidence put forth by Chen et al. suggests that pericytes have a potential therapeutic role in cardiac muscle regeneration as well [14]. Here, local human pericyte transplantation improved cardiac contractility and reduced left ventricular dilatation in acutely infarcted mouse hearts. This was found to be attributable to paracrine effects on improved microvasculature and reduced inflammation, and to a lesser extent direct cellular mechanisms (differentiation into cardiomyocytes). In summary, the utility of PSC for efforts in bone and muscle regeneration has been well documented in preclinical animal models.

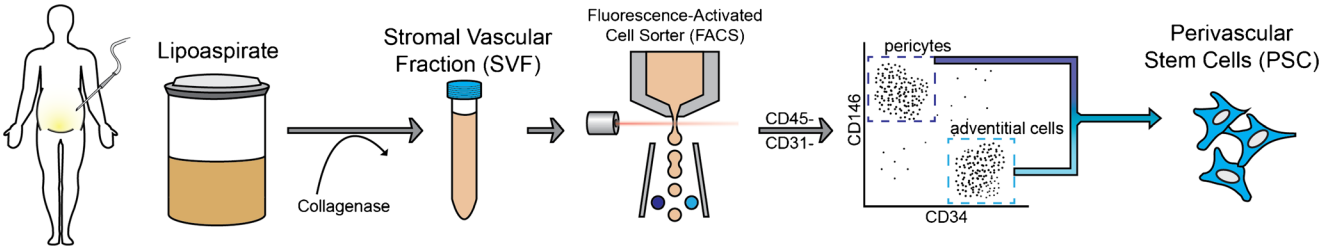

Fig. 1 Schematic of perivascular stem cell isolation. Fluorescence activated cell sorting can be used to identity two distinct PSC populations based on differential expression of perivascular markers: CD146+ pericytes and CD34+ adventitial cells. Cells are further isolated based on their negativity for CD45 and CD31. Both pericytes and adventitial cells express markers characteristic of culture-identified MSC

Pericytes and perivascular tumours

The 2002 WHO classification of soft tissue tumours recognizes two perivascular (pericytic) tumour types: glomus tumour and myopericytoma [15]. Previously, the diagnostic category of hemangiopericytoma (HPC) was also considered a perivascular tumour, but with the recent understanding of overlapping between HPC and solitary fibrous tumour (SFT), it is now considered within 'fibroblastic / myofibroblastic tumours.' Alternatively, Weiss and Goldblum categorize SFT/HPC under ‘tumours of uncertain type’ [16]. Both glomus tumour and myopericytoma are for the most part benign, subcutaneous tumours with a prominent perivascular growth pattern. In contrast, hemangiopericytoma/extrapleural SFT is composed of more immature appearing ovoid to spindled stromal cells, and are most commonly found in the deep soft tissues. The typical clinical presentation, histologic appearance, and evidence supporting pericytic/perivascular differentiation in these tumours are discussed sequentially below.

Glomus tumours typically involve the distal extremities, and most commonly the hands and feet [17]. However, glomus tumours have been reported in almost every part of the body [15]. First described by Masson in 1924 [18], the vast majority are small, typically less than 1 cm, red-blue painful subcutaneous nodules, and have a benign clinical course [19]. Atypical and/or malignant glomus tumours are rare, but are usually deep-seated, proliferative, larger tumours with cytologic atypia [20]. Several lines of evidence suggest a modified pericytic/modified smooth muscle phenotype for glomus tumour. First, the classic appearance of glomus tumour is that of small uniform glomus cells which are seen in a perivascular arrangement [16]. Even the common solid variant of glomus tumour has numerous intralesional blood vessels surrounded

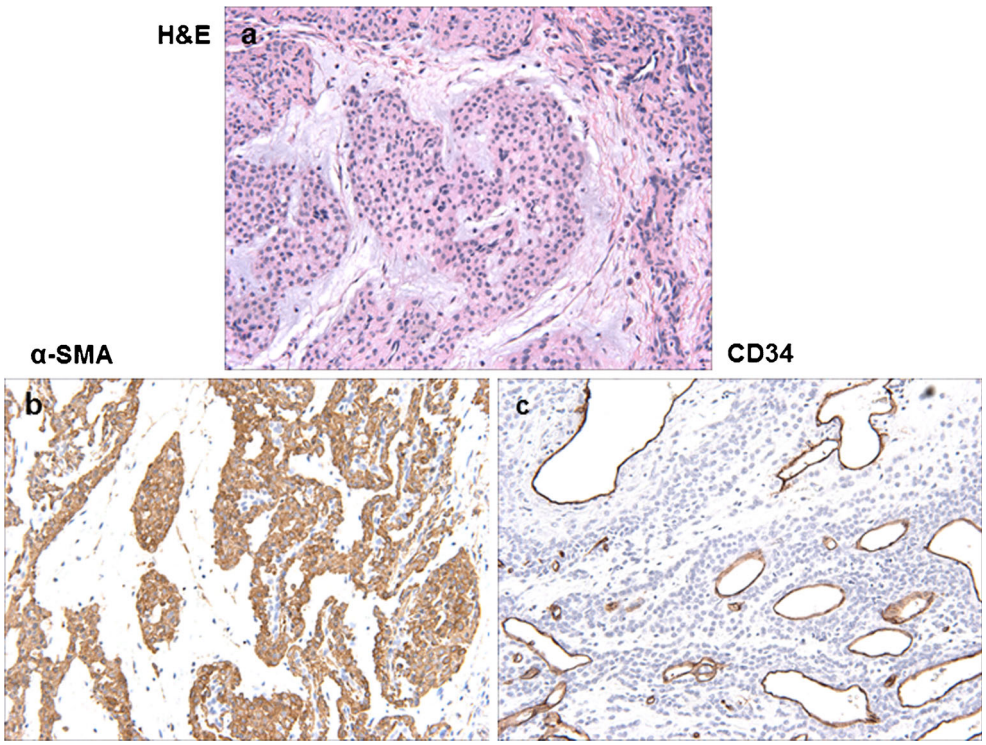

Fig. 2 Perivascular markers in glomus tumour. (**a**) Typical appearance as shown by H&E staining (20x). (**b**) αSMA immunostaining (20x). (**c**) CD34 immunostaining (20x)

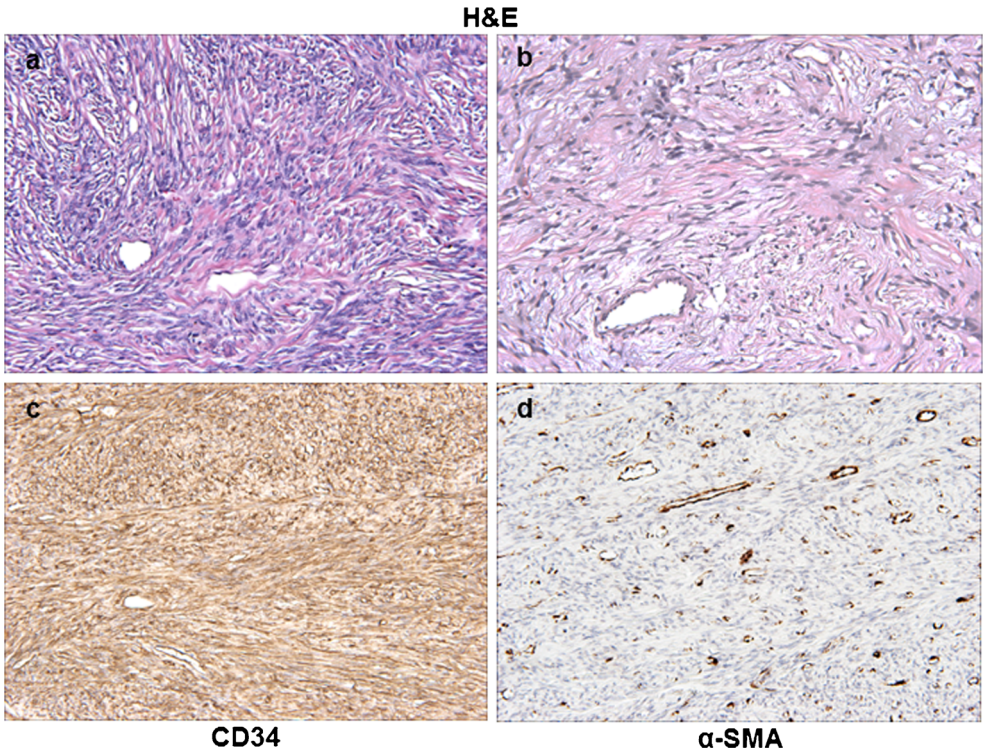

Fig. 3 Perivascular markers in extrapleural solitary fibrous tumour/hemangiopericytoma. (**a**, **b**) Typical appearance as shown by H&E staining (20x). Although the cellularity can vary, the overall cytomorphology is relatively similar between specimens. (**c**) CD34 immunostaining (20x). (**d**) αSMA immunostaining (20x)

by tumour cells [16]. The immunohistochemical phenotype of glomus tumour is relatively non-specific, but does support a pericytic/perivascular phenotype. This includes characteristic expression of α smooth muscle actin (αSMA) and vimentin in nearly all tumours, as do pericytes [20]. Focal CD34 expression can be seen in up to 20 % of tumours [20]. Some but not all glomus tumours are desmin positive [21]. However, a more detailed analysis of current pericyte markers in glomus tumour has not yet been performed. Some ultrastructural evidence via electron microscopy has shown smooth muscle and/or pericytic differentiation in glomus tumour. In general, ultrastructural studies of pericytes support a morphologic continuum between pericytes and smooth muscle cells [22]. Features of glomus cells include a scalloped nucleus, reminiscent of smooth muscle cells elsewhere in the body [22]. In addition and like smooth muscle cells, glomus cells contain many micropinocytotic vesicles and subplasmalemmal densities [22]. Moreover, the cytoplasm of glomus cells has a variable number of actin filaments, all features suggesting that they are modified smooth muscle cells [23]. Variants of classic glomus tumour exist, including glomangioma and glomangiomyoma (see [24] and [25] for a description). Atypical and malignant glomus tumour are very rare, typically deep-seated, and usually diagnosed by a combination of infiltrative growth pattern, atypia, and mitotic activity [20].

Myopericytoma is a benign, usually subcutaneous tumour of myoid appearing cells with a striking concentric perivascular growth pattern [15, 26]. Similar to glomus tumour, there is a predilection for myopericytoma to involve the distal extremities. The classic appearance of myopericytoma is that of relatively monomorphic oval to spindle shaped myoid cells that show a striking multilayered concentric growth around intralesional blood vessels [15]. The characteristic perivascular whorls of spindle cells are the tumours most diagnostic feature. Histological overlap between myopericytoma, glomus tumours, and hemangiopericytoma (see next) has been described [27]. The immunohistochemical analysis of myopericytoma generally includes αSMA and h-caldesmon positivity, which can be either diffuse or in a perivascular pattern [26, 27]. Like glomus tumour, focal CD34 immunostaining has been described [27]. Focal desmin expression can be observed, though not seen in glomus tumour. To our knowledge, an ultrastructural analysis of myopericytoma via electron microscopy has not yet been performed.

First described by Stout in 1942 and further clarified by Enzinger and Smith [28], the conceptual and diagnostic understanding of extrapleural solitary fibrous tumour/hemangiopericytoma has continued to evolve over the years. As alluded to previously, SFT/hemangiopericytoma is no longer categorized as a pericytic/perivascular tumour under the current WHO classification system [15]. The classic appearance of solitary fibrous tumour is of spindled to ovoid undifferentiated cells arranged in a so-called 'patternless pattern,' and which proliferate around and are intimately associated with prominent, thick-walled, often branching or "staghorn" vessels [15]. However, the histological appearance of SFT can be highly variable depending on the comparative cellularity and abundance of fibrous stroma. Ectopic differentiation has been

observed in SFT/hemangiopericytoma, including ectopic fat [29, 30], and very rarely ectopic cartilage or bone. These few case reports of ectopic mesenchymal differentiation suggest the possibility that some cells within SFT have mesenchymal stem cell properties. SFT/hemangiopericytoma is characteristically positive for CD34 (at least partially) and negative for αSMA [15]. It is worth noting that this is the characteristic opposite pattern as pericytes, which are CD34 negative, αSMA positive [31]. However, as previously mentioned, adventitial PSC are characteristically CD34 positive, and it is interesting to hypothesize their phenotypic overlap with lesional SFT cells [9, 31]. Various studies have examined the ultrastructural features of SFT/HPC [22]. In general, slender pericytes and pericyte cellular processes form concentric layers around the vascular spaces within SFT [22]. A distinguishing feature is that in SFT the pericytes share the basal lamina with the endothelial cells, while the cells of other tumour types lie outside the vascular basal lamina [22]. Transitional cells that lie on the morphological continuum between pericytes and smooth muscle cells are also seen [22]. Erlandson describes four discernable cell types within hemangiopericytoma, including the pericytelike cell, myoid pericyte, fibroblastlike cell, and undifferentiated mesenchymal cell [23]. This categorization of cell types within SFT again describes a morphological continuum between pericytes and smooth muscle cells. In fact, this heterogeneity in cell composition has led some investigators to conclude a more pluripotential perivascular cell as the cellular origin of SFT/hemangiopericytoma [4, 32]. However, the ultrastructural evidence supporting pericytic differentiation within SFT / hemangiopericytoma remains a debated topic, with some authors suggesting little to no evidence exists for true pericytic differentiation in SFT [15].

Perivascular invasion: a potentially under recognized route of spread for common malignancies

The importance of pericytes for limiting (or conversely facilitating) tumour spread has been recently uncovered. At least two potential roles have been examined: regulation of lymphovascular tumour spread and regulation of perivascular tumour migration. First, it has been well established that pericytes around tumour vessels have a more disorderly arrangement, along with aberrant cell shapes, change in marker expression, and looser vessel attachment [33–35]. Xian et al. more directly examined the role of pericytes in lymphovascular metastasis [36]. They identified NCAM mediated pericyte–endothelial interaction as important in limiting tumour vessel invasion. Moreover, pericyte deficient mice, or Pdgfb(ret/ret) mice, showed increased lymph node and distant organ metastasis. Thus, abnormal pericyte–endothelial cell interaction has clear ramifications on the ability of tumour cells to undergo lymphovascular invasion. In fact, the concept of using anti-angiogenic drugs to "normalize" tumour vessels and restore their protective pericyte function has attracted increased scientific attention [37].

Additionally, recent evidence points to a distinctly different mode of tumour spread from classic lymphovascular invasion: that of perivascular invasion or pericyte mimicry. This migration along the outer or abluminal aspect of vessels has been described in common malignancies of the skin, brain, and pancreas. For example, Lugassy et al. have described pericytic mimicry through the association of melanoma cells with the abluminal surfaces of vessels or angiotropism. Angiotropic melanoma cells spread along the abluminal surface of vessels in a pericytic location, i.e. along the abluminal vascular surface and without entering the vascular channels. This process has also been termed 'extravascular migratory metastasis' (EVVM) [38–40]. Similar findings have been shown in other solid tumours, notably in the malignant brain tumour, glioblastoma multiforme. Indeed, invasive glioblastoma cells are known to follow distinct anatomic structures within the central nervous system, including the abluminal surface of blood vessels, exhibiting the same phenotypic pericytic mimicry as angiotropic melanoma cells. For example, Cheng et al. described the ability of glioblastoma tumour cells to differentiate into pericyte-like cells [41]. Moreover, in examining human pathological specimens the majority of vessel lining pericytes could be identified as of glioblastoma cell origin. In summary, new data suggests that common malignancies utilize perivascular migration and associated pericyte mimicry as a potentially under-recognized route of tumour spread.

Conclusions

In conclusion, pericytes have a wide range of roles in health and disease. Far from being only important for blood pressure control, pericytes increasingly are thought to play an important role in tumour formation, growth, angioinvasion and metastases. Recent studies also show pericytes/PSC can differentiate along numerous mesenchymal lineages, including osteogenic, myogenic, chondrogenic and adipogenic lineages. In particular, the ability of pericytes to form bone, skeletal muscle and cardiac muscle makes them a focus of considerable interest for mesenchymal tissue engineering. Thus, the pericyte may prove to play a critical role in metastatic development and in treating important diseases of the skeletal and muscular systems.

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Conflict of interest The authors declare that they have no conflict of interest.

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