

## Review of Pericytes in Tumor Biology

Michelle A. Scott, Jia Shen, Karen Lam, Yu-Hsin Yen, Swati Shrestha, Marco Mravic, Greg Asatrian, Choon G. Chung, Claire Lugassy, Raymond L. Barnhill, Sarah M. Dry, Bruno Peault, Aaron W. James

Michelle A. Scott, Karen Lam, Yu-Hsin Yen, Marco Mravic, Bruno Peault, Aaron W. James, Orthopaedic Hospital Research Center, University of California, Los Angeles, USA

Michelle A. Scott, Jia Shen, Karen Lam, Yu-Hsin Yen, Swati Shrestha, Claire Lugassy, Raymond L. Barnhill, Sarah M. Dry, Aaron W. James, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA

Michelle A. Scott, Greg Asatrian, Choon G. Chung, Children's Hospital Los Angeles, Los Angeles, CA 90027, USA

Jia Shen, School of Dentistry, University of California, Los Angeles, USA

Correspondence to: Aaron W. James, MD, Department of Pathology & Laboratory Medicine, University of California, Los Angeles, David Geffen School of Medicine, 10833 Le Conte Ave., 13-145 CHS, Los Angeles, California 90095, USA.

Email: [Awjames@mednet.ucla.edu](mailto:Awjames@mednet.ucla.edu)

Telephone: +1-310-206-6754

Fax: +1-310-267-2058

Received: December 22, 2014

Revised: January 24, 2015

Accepted: January 30, 2015

Published online: June 23, 2015

### ABSTRACT

Pericytes are contractile cells that surround the endothelium of capillaries and venules throughout the body. Pericytes were once thought to have a limited role in blood pressure control and angiogenesis. Today, knowledge about pericytes and other perivascular stem cells has vastly expanded. The understanding of the biologic significance of pericytes was most changed by the recognition of the perivascular identity of mesenchymal stem cells. The following review article will summarize the known functions and importance of pericytes in particular relevance to tumor biology. These roles include: (1) pericytes as the potential cell of origin for multiple soft tissue tumors; (2) the role of pericyte in regulating tumor cell vascular invasion; and (3) angiotropism or 'pericytic mimicry' as a mechanism of malignant tumor spread. Although not discussed, the role of pericytes in pathophysiology far exceeds the

realms of tumor biology, including cardiovascular atherosclerotic disease, chronic kidney disease, fibrotic repair processes, and fibroproliferative diseases. In summary, the known roles of pericytes in tumor formation, growth, and invasion have greatly expanded. These include pericytic differentiation in soft tissue tumors, regulation of vascular invasion in solid tumors, and extravascular migratory migration of common malignancies.

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**Key words:** Pericyte; Perivascular stem cell; Glomus tumor; Myopericytoma; Solitary fibrous tumor; Pericyte mimicry; EVMM

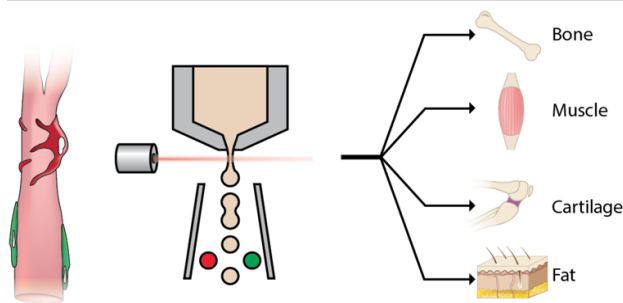
Scott MA, Shen J, Lam K, Yen YH, Shrestha S, Mravic M, Asatrian G, Chung CG, Lugassy C, Barnhill RL, Dry SM, Peault B, James AW. Review of Pericytes in Tumor Biology. *International Journal of Orthopaedics* 2015; 2(3): 301-306 Available from: URL: <http://www.ghrnet.org/index.php/ijo/article/view/991>

### INTRODUCTION

Pericytes are mural cells common to the microvasculature that enwrap endothelial cells. These supportive perivascular cells are essential to angiogenesis as well as tissue homeostasis, vessel permeability, and blood pressure control. In terms of angiogenesis, they have been found to be integral to blood vessel development both during development and in adulthood<sup>[1]</sup>. In recent years, the known roles of pericytes in tumor biology have vastly increased. For example, pericyte malfunction or loss has been associated with increased frequency of vascular invasion, and consequent metastatic disease<sup>[2,3]</sup>. Alternatively, tumor cells in several malignancies can circumvent intravascular invasion via adopting a pericyte-like phenotype (or pericyte mimicry) and migrating along the extravascular surface of vessels<sup>[4-6]</sup>. While accumulating evidence points to the pericyte as a key regulator of intravascular and extravascular tumor spread, the conceptual understanding of this is in evolution, as discoveries in stem cell biology and tumor biology continue to shape the field.

Substantial evidence points to pericytes as the native *in vivo* progenitors of mesenchymal stem cells (MSC)<sup>[7,8]</sup>. Three lines of evidence support this hypothesis: (1) MSC markers have been found to be co-expressed *in vivo* in a perivascular location, (2) purified pericytes give rise to multiple mesodermal tissues after *in vivo* transplantation, and (3) purified pericytes give rise to cells identical to MSC in culture<sup>[9,10]</sup>. Figure 1 highlights the conceptual understanding of pericytes and other perivascular stem cells (PSC) as MSC progenitor cells. In addition, the potential role of pericytes and other perivascular cells in soft tissue tumor biology has greatly increased<sup>[4,11]</sup>. Multiple lines of evidence suggest the possibility that pericytes and other PSC may be the putative cell of origin for several perivascular, mesenchymal tumors.

In this review, we discuss the diverse roles of pericytes in tumor biology. This includes the maintenance of tumor vasculature, role in vascular invasion and extravascular tumor migration. As well, select soft tissue tumors are discussed, owing to their architectural and cytologic resemblance to pericytes.



**Figure 1** Schematic of pericyte / perivascular stem cell location, purification and MSC properties. (Left) Perivascular cells including pericytes which closely enwrap the microvessels (red) and adventitial cells, which lie in the adventitia of larger vessels (green). (Center) Perivascular stem cells can be isolated by fluorescence activated cell sorting (FACS), by differential expression of CD146 and CD34. (Right) Both pericytes and adventitial cells demonstrate multilineage differentiation potential characteristic of MSC, including the ability to differentiate down osteogenic, myogenic, chondrogenic, and adipogenic lineages.

## PERICYTES IN TUMOR SPREAD

Two important roles for pericytes in tumor spread have been identified, including in (1) vascular invasion and (2) angiotropism/pericyte mimicry. Each is discussed separately below.

### Pericytes implicated in vascular invasion

Multiple lines of evidence suggest that pericytes play a naturally protective role against vascular invasion by tumor cells. First, established evidence has shown that pericytes around tumor vessels demonstrate a more disorderly arrangement, cell shape abnormalities, and loosened attachment<sup>[12-14]</sup>. These findings have been verified ultrastructurally. By electron microscopy, tumor associated pericytes have been observed to have increased distance from associating blood vessels as well as abnormal cytoplasmic processes and endothelial interactions<sup>[15,16]</sup>. This incomplete coverage and loosened endothelial - pericyte interaction are thought to result in increased vascular permeability. In fact, reduced pericyte coverage along tumor associated vessels has been associated with poor prognosis in breast ductal adenocarcinoma<sup>[17]</sup>. These structural and ultrastructural changes are associated with abnormal protein marker expression in tumor associated pericytes. For example, aberrant desmin immunoreactivity was found in pericytes associated with pancreatic adenocarcinoma - a rare finding in normal pancreatic pericytes<sup>[15]</sup>.

Multiple investigators have targeted pericytes or the pericyte - endothelial cell complex in the context of tumor biology and observed increased vascular permeability, increased tumor cell vascular invasion, and tumor metastasis. Xian *et al* examined the role of pericytes in limiting vascular invasion in a mouse pancreatic  $\beta$  cell tumor model<sup>[3]</sup>. NCAM (neural cell adhesion molecule) deficient mice displayed perturbed pericyte - endothelial cell interaction, resulting in increased vascular permeability and pancreatic  $\beta$  cell tumor cell metastasis<sup>[3]</sup>. This finding was also extended to mice deficient in pericytes themselves, using  $Pdgfb^{ret/ret}$  mice. Here, loss of pericytes in the  $Pdgfb^{ret/ret}$  mouse resulted in significant and widespread pancreatic  $\beta$  cell tumor metastasis. Conversely, aberrant upregulation of NCAM had the reverse effects, limiting vascular invasion and metastatic potential<sup>[3]</sup>. Cooke *et al* studied the effects of pericyte deficiency in breast adenocarcinoma metastasis, with strikingly similar findings. Here, the investigators used a transgenic mouse that allowed for selective ablation of NG2+ pericytes using ganciclovir treatment<sup>[17]</sup>. While pericyte depletion slowed tumor growth, it also increased the rate of vascular invasion and distant carcinoma metastasis. Similar results were found by selective ablation of another pericyte marker, PDGFR- $\beta$  (platelet derived growth factor receptor- $\beta$ )<sup>[17]</sup>. Likewise, pharmaceutical inhibition of PDGFR- $\beta$  using two tyrosine kinase inhibitors (Imatinib and Sunitinib) replicated the findings of genetic pericyte ablation, including decreased pericyte coverage, altered vascular structures, and increased rate of tumor metastasis. Recently, investigators have attempted to subcategorize pericytes by cell surface marker expression. For example, Birbair *et al* has described type 1 and 2 pericytes based on differential expression of Nestin and NG2<sup>[18]</sup>. Interesting type 2 pericytes only seem to participate in tumoral angiogenesis in this model, although selective targeting of type 2 pericytes has not yet been employed<sup>[18]</sup>. Thus, across multiple carcinoma models, the targeting of pericytes or the pericyte - endothelial cell interaction results in increased vascular permeability, increased vascular invasion, and consequent metastasis.

Disruption or dissociation of pericytes from their endothelial cells also results in an hypoxic tumor microenvironment, which in some models favors tumor cell epithelial-to-mesenchymal transition (EMT) and increased tumor invasiveness<sup>[19]</sup>. Overexpression of hypoxia-inducible factor-1alpha (HIF-1 $\alpha$ ) has been shown to activate the EMT master regulator TWIST by binding to a hypoxia response element in the TWIST promoter<sup>[20]</sup>.

Similarly, HIF-1 $\alpha$  also binds to the Met promoter and upregulates expression of this hepatocyte growth factor (HGF) receptor protein, promoting tumor invasion<sup>[21,22]</sup> and EMT<sup>[22]</sup> in multiple cancer cell lines *in vitro*. These findings have also been extended to tumor hypoxia induced by pericyte deficiency. Cooke *et al.* found that selective pericyte ablation, as previously discussed by either genetic or pharmaceutical methods, led to increased expression of HIF-1 $\alpha$  and Met as well as a transcriptional profile consistent with a mesenchymal rather than epithelial program (EMT)<sup>[17]</sup>. Thus, selective pericyte ablation likely has multiple effects favoring tumor metastasis, including increased vascular permeability favoring vascular invasion, but also hypoxia induced EMT favoring tumor cell invasiveness.

In addition, multiple lines of evidence suggest that pericytes play a role in resistance to anti-angiogenic therapy. Overall, it appears that vessels without pericyte coverage (or 'naked' vessels) are more susceptible to VEGF-targeted agents<sup>[23]</sup>. In contrast, mature vessels with pericyte coverage seem to persist in the setting of anti-VEGF agents<sup>[24-26]</sup>. This observation has led to the concept of combination therapy using both VEGF and PDGFR inhibitors<sup>[25,26]</sup>. It appears that

in many clinical scenarios, combination anti-VEGF/anti-PDGFR approaches are more effective in pruning tumor vessels than either approach alone<sup>[25,26]</sup>. However, this combinatorial effect has not been observed by all investigators<sup>[27,28]</sup>.

#### Pericyte mimicry / Extravascular migratory metastasis

Conversely, a novel paradigm for metastasis has been described within the past 15 years. Apart from the classical mechanism of lymphovascular invasion, extravascular migratory metastasis (EVMM) leads to metastasis without tumor cell entry into the blood stream. During EVMM, angiogenic tumor cells migrate in a 'pericytic-like' manner along the external or abluminal surfaces of vascular channels, without intravasation. By this mechanism, tumor cells may spread to nearby or more distant sites. In doing so, these tumors adopt the position of perivascular cells, particularly the pericyte<sup>[5,29]</sup>. Pericyte mimicry has been documented in common malignancies of the skin, brain, pancreas, and prostate.

Pericyte mimicry, or angiotropism, has been most thoroughly studied in melanoma<sup>[5,6,14,29-31]</sup>. Lugassy *et al* first described the pericyte-like position of invading melanoma cells along the blood vessel basal lamina<sup>[32-34]</sup>. In fact, 91% of cases of human melanoma reviewed in another study did not have a clearly defined basement membrane<sup>[35]</sup>. Building on these findings, human melanoma cells were shown to localize to both endothelial tubules formed *in vitro* as well as invade in a perivascular fashion when injected *ex vivo* into the brains of mice<sup>[6,36]</sup>. Pericyte mimicry in melanoma has been confirmed at the immunophenotypic level, where angiogenic melanoma cells express pericyte antigens PDGFR- $\beta$ , NG2, and CD146<sup>[30]</sup>. Further, microarray analysis showed increased expression of PDGF- $\beta$  after migration of melanoma cells along the abluminal surface of endothelial tubules during the co-culture of endothelial cells and melanoma cells<sup>[30]</sup>, indicating increased expression of a receptor key in the endothelium's recruitment of pericytes. Additionally, the interaction between the abluminal endothelial tubules and angiogenic melanoma cells induced differential expression of malignancy associated genes, linked to metastasis (CCL2, ICAM1 and IL6) and disease progression (CCL2, ICAM1, SELE, TRAF1, IL6, SERPINB2 and CXCL6)<sup>[30]</sup>. Angiotropism has been shown to be clinically quite relevant, as angiotropism is a poor prognostic indicator in malignant melanoma<sup>[37]</sup>.

Recently, Bald *et al* used HGF overexpressing mice with impaired cell cycle control and predisposition toward development of melanoma<sup>[31]</sup>. Chemically-induced melanoma formation was followed by UV exposure, causing melanoma cell to invade via the abluminal surfaces of blood vessels<sup>[31]</sup>. Overall, intermittent intense UV exposure stimulated angiogenesis, melanoma cell motility, and increased melanoma-endothelial cell interaction<sup>[31]</sup>. This important finding indicates that neutrophil-rich inflammatory response increases angiotropism, pericytic mimicry and metastasis, paving the way for future experimental manipulation. Importantly, in the molecular study mentioned above<sup>[22]</sup>, ten genes directly linked to inflammation were upregulated (CCL2, IL6, TRAF1, CXCL6, SELE, ICAM1, SERPINB2, SLC7A2, C2CD4B, PDGFB), raising important questions about whether inflammation is the cause or the result of such gene expression in angiogenic melanoma.

Fascinating parallels have been drawn between angiotropism of melanoma cells and that of malignant glial cells in glioblastoma. Among the routes of glioblastoma spread, migration along the abluminal surface of blood vessels has been well documented<sup>[38]</sup>. Indeed, transplanted glioma cells (GL26 murine glioma cell line) adopt an angiogenic distribution<sup>[6]</sup>. This gradual adoption of an

angiogenic location of glioma cells was observed either in culture with capillary-like matrigel cultures, or after direct injection into the mouse brain<sup>[6]</sup>. In all cases, the glioma cells did not enter the luminal space, but instead remained in a pericytic location. These experimental findings are consistent with the fact that even the most malignant glial tumors generally do not penetrate the vascular basement membrane<sup>[38]</sup>. Cheng *et al* further delineated the phenomenon of pericyte mimicry in high grade glial tumors in an experimental mouse model<sup>[39]</sup>. Using *in vivo* lineage tracing, Cheng showed that glioblastoma stem cells (GSC) can adopt an immunophenotype similar to pericytes. Moreover, GSC were found to generate  $\alpha$ SMA+ ( $\alpha$ Smooth Muscle Actin) pericyte-like cells *in vivo*<sup>[39]</sup>. For this reason, when observing human pathological specimens, a glioblastoma cell origin was identified for the vast majority of intra-tumoral pericyte cells. Moreover, pericytic cells outside the glial tumor were identified to have GSC markers - another experimental model of angiotropism. Recent studies in GBM have in fact found that GBM cell angiotropism is associated with dramatic changes in the structure of pre-existing blood vessels, termed 'vessel co-option'<sup>[40]</sup>. This change in vessel morphology was associated with intimate connections between GBM (glioblastoma multiforme) cells and native pericytes, resulting in altered contractility of the pericytes themselves<sup>[40]</sup>. Other investigators have examined the importance of CNS (central nervous system)-specific pericyte cytokine both in the maintenance of the blood brain barrier<sup>[41]</sup>, and chemokine elaboration and the probable crosstalk between CNS pericytes and tumors, especially in the context of inflammation and hypoxia<sup>[42,43]</sup>.

In addition, pancreatic and prostate adenocarcinomas have also display angiotropism. For example, angiotropism has been documented in several cases of prostatic adenocarcinoma<sup>[14]</sup>. Remarkably, angiotropism was detected in all cases examined of prostatic adenocarcinoma, at least focally. These findings were recapitulated both *in vitro* and *in vivo* using the prostate carcinoma cell line PC3. Using a co-culture method with capillary like structures, PC3 cells gradually adopted a perivascular distribution with time in culture. Similar findings were seen *in vivo* in a chick chorio-allantoic membrane (CAM) model. After injection of GFP labeled PC3 tumor cells, a propensity for the PC3 cells to associate with the perivascular space was again observed<sup>[44]</sup>. Similarly clinical correlates have been described in pancreatic adenocarcinoma<sup>[44]</sup>. In case reports, soft tissue metastases encircling the celiac artery and its branches have been reported as an example of EVMM in pancreatic adenocarcinoma. These findings were verified by endoscopic ultrasound guided fine needle aspiration (FNA)<sup>[44]</sup>. All sum, these new data suggest that common malignancies of the skin, brain, pancreas and prostate all show evidence of pericyte mimicry/EVMM as a mode of tumor spread.

## PERIVASCULAR CELLS AS MESENCHYMAL STEM CELL PROGENITORS

In recent years, *in vivo* localization of MSC has been accomplished, showing that the native residence of MSC is clearly in a perivascular location<sup>[9]</sup>. Indeed, immunofluorescent co-expression of MSC markers (including CD44, CD90, CD73, and CD105) align with classic pericyte markers, such as CD146<sup>[9]</sup>. As mentioned, purified pericytes have demonstrable MSC characteristics at the clonal level, including expression canonical MSC markers, and exhibition of multilineage mesodermal differentiation potential<sup>[9]</sup>. Pericytes have been documented to give rise to several cell types *in vivo* such as dendritic cells<sup>[45]</sup>, white adipocytes<sup>[10]</sup>, and skeletal satellite cells<sup>[46]</sup>



(Figure 1). Despite these studies, there remains much debate about the pericytic origin of mesenchymal stem/progenitor cells in both development and in adult tissue repair and maintenance<sup>[8,11]</sup>.

Interestingly, a second population of perivascular cells has been more recently identified with MSC attributes, termed adventitial cells. These cells are so named as they reside in the tunica adventitia, unlike pericytes which closely contact the abluminal surface of endothelium<sup>[47]</sup>. With divergent expression of cell surface markers, these CD34<sup>+</sup>CD146<sup>-</sup>CD31<sup>-</sup> perivascular stem cells are distinct from pericytes, but exhibit similar MSC properties<sup>[47]</sup>. Currently, PSC have been examined as a plentiful source of adult MSC for musculoskeletal tissue regeneration<sup>[8,48,49]</sup>.

In terms of tumor biology, the capability of perivascular MSC such as pericytes to self-renew implicates PSCs as potential cells of origin of many perivascular mesenchymal tumors<sup>[4]</sup>.

## PERICYTES IN TUMORIGENESIS

The pericytic/perivascular family of soft tissue tumors are generally composed of modified vascular smooth muscle cells. These consist of glomus tumor and its variants, myopericytoma, and solitary fibrous tumor / hemangiopericytoma (SFT/HPC). The clinical and histologic representation, as well as the possibility of perivascular origin is described below. Also discussed is the PEComa (perivascular epithelioid cell tumor) family of tumors, with dual myoid-melanocytic differentiation.

### Classic (Sporadic) Glomus Tumor

Classic glomus tumor are predominantly benign, subcentimetric, red-blue nodules, that histologically resemble the thermoregulatory glomus body<sup>[50]</sup>. They are most often located subcutaneously, typically on the distal upper extremities and most often in a subungual location<sup>[51,52]</sup>. Pain with temperature sensitivity is a common finding. Histologically, glomus tumors demonstrate a variably prominent perivascular growth pattern (Figure 2). This architectural feature, combined with smooth differentiation by immunohistochemical and electron microscopy shows some overlap with microvascular pericytes. For example, glomus cells demonstrate immunoreactivity for vimentin and  $\alpha$ -smooth muscle actin. As well,

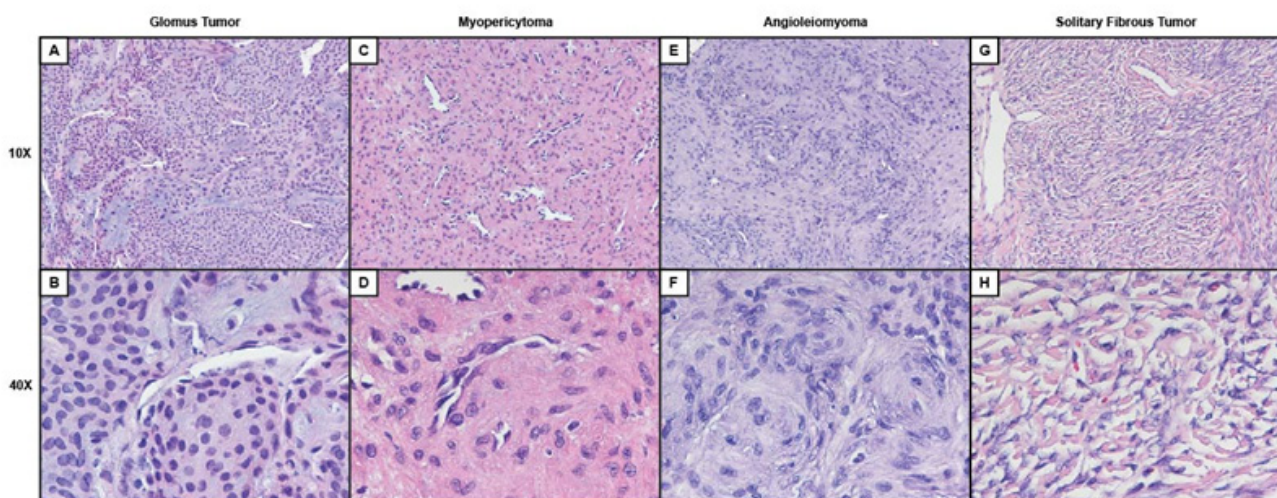
electron microscopy reveals abundant cytoplasmic actin filaments and numerous superficial pinocytotic vesicles, again suggestive of modified pericytic or smooth muscle differentiation<sup>[53,54]</sup>. The extent to which glomus cells retain properties of pericytes has not yet been explored, such as attributes similar to MSC.

### Glomus tumor variants

A number of glomus tumor variants diverge from the typical appearance and presenting features of glomus tumor, yet still express similarity in perivascular tumor growth and pericytic/myoid immunophenotype. One variant, known as glomuvenous malformation or glomangioma, is made up of typical glomus cells, but has an architecture more similar to a cavernous hemangioma. Lesions generally arise during childhood and are less painful than typical glomus tumor<sup>[50]</sup>. Another variant, glomangiomyoma, displays partial or focal smooth muscle differentiation and lies on a spectrum with similarity to angiomyoma. Glomangiomas (diffuse glomus tumor) are extremely rare, diffuse, infiltrative lesions typically associated with adipose tissue<sup>[50]</sup>. Atypical and malignant glomus tumors are exceedingly rare, deep-seated, proliferative, larger tumors. Folpe et al. proposed the following classification scheme for malignancy in glomus tumor: deep-seated location and a size > 2 cm, or atypical mitotic figures, or moderate to high nuclear grade and  $\geq 5$  mitotic figures/50 hpf<sup>[55]</sup>.

### Myopericytoma

Myopericytoma is a benign, painless, well circumscribed tumor with pericytic/smooth muscle differentiation. Unlike glomus tumor, myopericytomas are most often dermal or subcutaneous tumors typically found on the lower extremities and more common in men. Much like glomus tumor, the histological picture is that of a perivascular proliferation of myoid cells. However, myopericytoma typically has a whorling perivascular pattern of tumor cell arrangement (Figure 2). Cytologically, myopericytoma cells have less conspicuously enlarged nuclei and more eosinophilic cytoplasm than glomus cells. Electron microscopy reveals evidence of pericytic/myoid differentiation, including thin filaments, subplasmalemmal densities, and pinocytotic vesicles<sup>[54]</sup>.



**Figure 2** Histological appearance of pericytic soft tissue tumors. (A,B) Typical appearance of glomus tumor, including rounded tumor cells arranged in a solid to perivascular arrangement with focal stromal myxoid change. (C,D) Typical appearance of myopericytoma, including a perivascular proliferation of cells with ovoid nuclei and abundant eosinophilic cytoplasm. (E,F) Typical appearance of the angioleiomyoma – similar to myopericytoma, angioleiomyoma consist of tumor cells with smooth muscle differentiation and an angiocentric growth pattern. (G,H) Typical appearance of solitary fibrous tumor (SFT), including a low grade proliferation of spindle cells on a variably fibrotic background, with large branching blood vessels.

### Solitary Fibrous Tumor (SFT)/Hemangiopericytoma (HPC)

Before 2002, hemangiopericytoma (HPC) was considered by most sources a perivascular neoplasm. Currently, the WHO (World Health Organization) considers solitary fibrous tumor (SFT) and HPC along a spectrum of tumors with overlapping morphology and demonstrating CD34 immunoreactivity. The typical appearance is that of spindled cells arranged in a so-called 'pattern-less pattern,' set in variable amounts of fibrous stroma with prominent, branching (or staghorn-shaped) blood vessels (Figure 2). In general, SFT / HPC is not considered a lesion of pericytes, which are generally CD34 negative. The exception to this is potentially in the sinonasal region (discussed below).

### Hemangiopericytoma-Like Tumor of Nasal Passages (HTNP)

Unlike the typical SFT / HPC, hemangiopericytoma-like tumor of nasal passages (HTNP) is a distinct entity which arises in the nasal passages, often in female patients<sup>[50]</sup>. The histologic appearance of HTNP is similar to typical SFT/HPC, although only a minority of HTNP demonstrate CD34 immunoreactivity<sup>[56]</sup>. Indeed, morphological and immunohistochemical similarities to glomangiopericytoma of soft tissue has led some to adopt the term glomangiopericytoma as a more accurate classification<sup>[57]</sup>. Although some investigators have considered HTNP to display true pericytic / myoid differentiation<sup>[58]</sup>, a comprehensive evaluation of this has not yet been performed.

### PEComa family of tumors

Unlike other perivascular myoid tumors previously discussed, the PEComa family tumors are a unique group of diverse tumors with dual smooth muscle and melanocytic differentiation and unknown histogenesis<sup>[50,59]</sup>. Renal and extrarenal angiomyolipomas are most common PEComa family tumor. Other variants include lymphangiomyomatosis, clear cell sugar tumor of the lung, and others. Tumor cells may be either epithelioid or spindled, but all PEComa family tumors are characterized by their prominent perivascular growth pattern and dual myomelanocytic differentiation. Interesting theoretical parallels can be drawn between angiotropic melanoma, discussed earlier, and PEComa. However, while angiotropism is associated with a poor prognosis in malignant melanoma<sup>[37]</sup>, PEComa family tumors are defined by their vasculocentric growth and a similar prognostic significance for this growth pattern has not been established.

## SUMMARY

Far from being inert bystanders in tumorigenesis and tumor spread, pericytes and other perivascular stem cells have significant function in tumor biology. As their biologic relevance continues to expand, more and more investigators have turned to pericytes as potential regulators of local and distant tumor spread. Pericytic regulation of tumor spread has been studied across diverse malignancies, including melanoma, various adenocarcinomas, and glioblastoma, to name a few. In particular to regulation of tumor spread, it seems that pericytes play at least a dual role: including (1) prevention/regulation of vascular invasion, but also (2) probable regulation of angiotropism/pericyte mimicry. From these standpoints, methods to reinforce the pericyte - endothelial cell interaction may be an important future adjunct to traditional chemotherapeutic agents. As investigators have already shown, pericytes may be subcategorized based on cell surface marker expression. Selected targeting of pericyte subpopulations may be a future promising avenue for tumor-specific effects. Finally in

terms of tumorigenesis, several lines of evidence suggest pericytic differentiation in a number of soft tissue tumors. While interesting to posit that the pericyte is the cell of origin for select perivascular / mesenchymal tumors, further investigation in this area is required.

## ACKNOWLEDGEMENTS

AWJ was supported by the UCLA Pathology Translational Research Fund. We thank AS James for his excellent technical assistance.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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- Peer reviewer:** Nupura Sudhir Bhise, Harvard/MIT Health Sciences & Technology Division, 288 Prospect Street, Apt. 5, Cambridge, USA