


Perivascular Cells

Prof. Steven S. Saliterman
Department of Biomedical Engineering, University of Minnesota
<http://saliterman.umn.edu/>

Perivascular cells

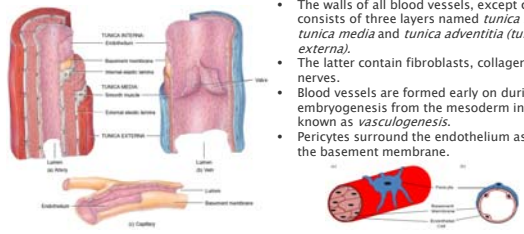


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Perivascular cells and tissue engineering: Current applications and untapped potential
Elisa Avolio^{1,2}, Valeria V. Ahvino³, Mohamed T. Gherbet³, Paola Campagnolo^{1,2,4*}

* Division of Experimental Cardiovascular Medicine, Bristol Heart Institute, University of Bristol, United Kingdom
† Division of Congenital Heart Surgery, Bristol Heart Institute, University of Bristol, United Kingdom
‡ School of Biomedical Sciences, University of Exeter, Exeter, United Kingdom

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Vascular Anatomy



- The walls of all blood vessels, except capillaries, consists of three layers named *tunica intima*, *tunica media* and *tunica adventitia* (*tunica externa*).
- The latter contain fibroblasts, collagen and nerves.
- Blood vessels are formed early on during embryogenesis from the mesoderm in a process known as *vasculogenesis*.
- Pericytes surround the endothelium as part of the basement membrane.

Image Courtesy of John Wiley & Sons

Mills, S. J., A. J. Cowin, and P. Kaur. "Pericytes, Mesenchymal Stem Cells and the Wound Healing Process." *Cells* 2, no. 3 (2013): 621-34.

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Pericytes

- ▶ Pericytes have stem cell-like properties and are seemingly able to differentiate into adipocytes, chondrocytes, osteoblasts and granulocytes, leading them to be identified as mesenchymal stem cells (MSCs).
- ▶ They increase ECs proliferation/survival and migration.
- ▶ They release a large variety of GFs and cytokines.
- ▶ They may accelerate wound healing.
- ▶ There are several markers, none unique, and vary with location and time.

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Marker Expression

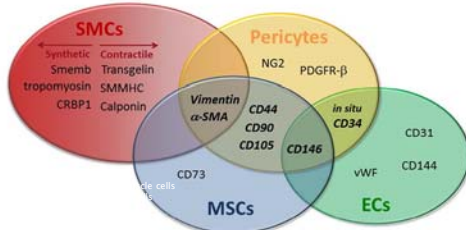
Table 1
Comparison of marker expression between mesenchymal stem cells (MSC), vascular smooth muscle cells (SMC), pericytes and endothelial cells (EC).

Cell type	Source	Phenotype	Reference
MSCs	Bone marrow, adipose tissue, peripheral blood, other tissues	CD44 + CD90 + CD105 + CD73 + CD146 + CD34 - CD45 - CD31 -	Hain et al. (2011)
SMCs	Arteries, veins	Synthetic: vimentin + α -Smeb + tropomyosin + CRBP1 + α -SMA + β -Tubulin + SMMHC + α -Actinin SMA + PDGFR + vimentin +	Wang et al. (2014) Campagnolo et al. (2010)
Pericytes and pericyte-associated cells	Capillaries/arterioles from various tissues	CD146 + α - CD34 + α - CD44 + CD90 + CD105 + CD73 + CD31 - CD45 - CD34 -	Chen et al. (2013) Avolio, Salterman et al. (2013)
ECs	Vascular intima	CD31 + CD146 + vWF + CD34 + CD45 -	Benigni et al. (2004)

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Expressed Markers & Overlap



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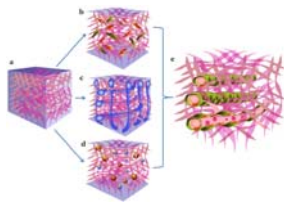
Table 2
Characteristics of progenitor and pericyte-associated isolated from different sources

Progenitor and source	Strategy of isolation	Phenotype in culture	Characteristics in function	References
Subepithelial stem pericytes (SPCs) from adipose tissue	CD34 + CD31 - magnetic bead selection	Positive: NC2, PDGFR β , CD34, CD38, CD49b, CD73, SH2B3, CD45, CD90, CD146, CD166, CD248, CD271 Negative: CD34, CD45, CD49b, CD73, PDGFR α , PDGFR β	Substitution control, blood vessel permeability, blood pressure regulation, angiogenesis, fibrocytic/epithelial repair process	Castrogonzalez et al. (2016)
Cardiac progenitor-associated (CPAs) from neonatal aortic vasculature	CD34 + CD31 - magnetic bead selection	Positive: NC2, PDGFR β , CD34, CD38, CD49b, CD73 Negative: CD34, CD45, CD90, CD146, CD166, CD248, CD271	Angiogenesis, VEGF-stimulated secretion	Avolio, Rodriguez-Rubalcaba, et al. (2017)
Mesodermal pericytes (MPs) from fetal adult heart	CD46 + CD34 - CD45 - CD31 - CD49b - CD146 - Fluorescent activated cell sorting	Positive: NC2, PDGFR β , CD34, CD38, CD49b, CD73, SH2B3, CD45, CD90, CD146, CD166, CD248, CD271 Negative: CD34, CD45, CD90, CD146, CD166, CD248, CD271	Angiogenesis, vascular permeability control, blood flow regulation, oxygen homeostasis, VEGF-stimulated secretion	Chen et al. (2013)
Vascular muscle pericytes (VMPs) from fetal adult heart	CD146 + CD34 - Fluorescent activated cell sorting	Positive: CD34, CD38, CD49b, CD73, SH2B3, CD45, CD90, CD146, CD166, CD248, CD271 Negative: CD34, CD45, CD90, CD146, CD166, CD248, CD271	Angiogenic potential, VEGF-stimulated secretion and VEGFR2 expression, VEGFR2 expression of pericytes is essential for vessel growth, Control of BBB integrity	Chen et al. (2008)
Bone pericytes (BPs) from bone microvasculature	Cloning and morphology	Positive: PDGFR α , SH2B3, NC2, NC1, NC3, NC4, NC5, NC6, NC7 Negative: CD34, CD45, CD90, CD146, CD166, CD248, CD271	Regulation of bone mineral architecture, VEGF-stimulated secretion, Regulation of osteoblast function and bone repair, Hemopoietic niches	Winkler et al. (2007), Winkler, et al. (2010), Winkler (2011)
Uterine pericytes (UPs) from human uterus	Density gradient or Fluorescent sorting based on endogenous control or bone morphogenetic protein	Positive: SH2B3, NC2, NC3, NC4, NC5, NC6, NC7 Negative: CD34, CD45, CD90, CD146, CD166, CD248, CD271	Remodelling and angiogenesis, VEGF-stimulated secretion, Angiogenesis and structural remodeling	Winkler and Noll (2007), Winkler et al. (2009), Winkler et al. (2010), Winkler et al. (2010), Winkler (2011)
Dermal pulp pericytes (DPPs) from dermal pulp	SH2B3 + magnetic bead selection	Positive: CD34, CD45, CD90, CD146, CD166, CD248, CD271 Negative: VEGF	High proliferative potential, Regeneration of vascularized structure in bone and dermal repair/angiogenesis	Yu and Greenhalgh (2005), Avolio, et al. (2017)

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Strategies for Vascularization

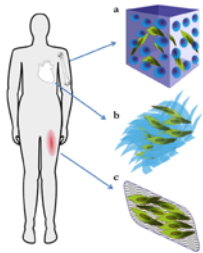


- a) Uniform vascularization.
- b) Combination of the material with cells able to support angiogenesis.
- c) Design of the scaffold structure reproducing vascular like-structures that will act as a guide for the angiogenic process.
- d) Incorporation of angiogenic factors during the manufacture of the graft.
- e) The result should be a vascularized graft in which new-formed vessels are mature and functionally competent.

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Perivascular Cells for Damaged Tissues



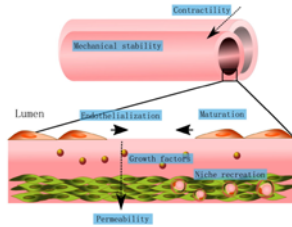
- a) Bone reconstruction was achieved by incorporating PCs in 3D scaffolds.
- b) Heart patches obtained by stacking multilayers of PCs combined grown on matrix substrate were devised for myocardial infarction.
- c) Topical application of dermal patches containing PCs improved skin wound healing.

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Role of Perivascular Cells in TE Grafts

1. The seeding of vascular grafts with perivascular cells increases their contractility and mechanical properties, regulating permeability.
2. The release of growth factors by the perivascular cells regulates endothelialization and endothelial cell function.
3. Additionally, perivascular cells contribute to the reconstitution of the perivascular niche, favoring the long-term graft success.



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Summary

- ▶ Pericytes have stem cell-like properties and are mesenchymal stem cells.
- ▶ They promote vessel growth and stability.
- ▶ May in the future be useful for vascular graft repopulation, and skeletal and cardiac muscle grafts.
- ▶ May be an alternative to bone marrow mesenchymal stem cells (BMSCs) for bone regeneration.

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