Chapter 10
Pericytes in Tissue Engineering

Betül Çelebi-Saltik

Abstract Pericytes have crucial roles in blood-brain barrier function, blood vessel function/stability, angiogenesis, endothelial cell proliferation/differentiation, wound healing, and hematopoietic stem cells maintenance. They can be isolated from fetal and adult tissues and have multipotential differentiation capacity as mesenchymal stem cells (MSCs). All of these properties make pericytes as preferred cells in the field of tissue engineering. Current developments have shown that tissue-engineered three-dimensional (3D) systems including multiple cell layers (or types) and a supporting biological matrix represent the in vivo environment better than those monolayers on plastic dishes. Tissue-engineered models are also more ethical and cheaper systems than animal models. This chapter describes the role of pericytes in tissue engineering for regenerative medicine.

Keywords Pericytes · Tissue engineering · Mesenchymal stem cells · Hematopoietic stem cells · Niche · Scaffold · Bone tissue engineering · Cartilage tissue engineering · Dermal tissue engineering · Vascular tissue engineering · Cardiac tissue engineering · Blood tissue engineering

Introduction

Mesenchymal stem cells (MSCs) have attracted considerable attention as therapeutic cells for regenerative medicine although they are heterogeneous population. It has been described that MSCs originate from two types of perivascular cells, namely, pericytes and adventitial cells, which contain the in situ counterpart of MSC in developing and adult human organs, which can be purified using defined cell

---

B. Çelebi-Saltik (✉)
Department of Stem Cell Sciences, Hacettepe University Graduate School of Health Sciences, Ankara, Turkey

Center for Stem Cell Research and Development, Hacettepe University, Ankara, Turkey
e-mail: betul.celebi@hacettepe.edu.tr

A. Birbrair (ed.), *Pericyte Biology - Novel Concepts*, Advances in Experimental Medicine and Biology 1109, https://doi.org/10.1007/978-3-030-02601-1_10

surface markers [26]. The French physiologist, Charles-Marie Benjamin Rouget identified pericytes as “non-pigmentary adventitial cells” or “intramural pericytes” in 1873, while the German anatomist Karl Wilhelm Zimmermann renamed them as “pericytes” in 1923 [3, 51]. By these expression patterns, pericytes can be separated from other perivascular cells like adventitial cells that are negative for CD146 and positive for CD34 [24]. The majority of pericytes are derived from mesoderm, whereas those found in the retina and brain are derived from the neural crest [48]. These cells are found in capillaries, arterioles, and venules as well as in the subendothelial regions of large-diameter blood vessels (Fig. 10.1) [2]. They engage with endothelial cells through special linkage units and paracrine signals and can increase the proliferation and provide effective endothelialization [35]. They are responsible for the regulation of vascular development, maturation, stabilization, blood flow, and pressure located in the periphery of the vessel wall [29]. Morphologically, pericytes are fibroblast-like cells with prominent nuclei, narrow cytoplasm, and many extensions [48]. Similarities have been described to exist between MSC and pericytes in terms of phenotype and gene expression, suggesting that MSCs indeed represent a progeny of the perivascular cell compartment [25]. Moreover, if one sorts culture expanded human pericytes for the in vivo marker CD146 or smooth muscle actin, the cells obtained have all of the classic markers for human MSCs (CD105, CD90, CD73) [27]. Most pericytes express neural/glial antigen 2 (NG-2) and platelet-derived growth factor receptor beta (PDGFR-β) and lack the expression of hematopoietic and endothelial markers, such as CD45 and CD31 [10, 19]. Although no marker is specific for pericytes, collectively these markers appear to selectively identify an MSC-like pericyte. The purification of pericytes is described as a CD146+CD34-CD45- cell population [42]. Caplan mentioned that these cell sorts clearly documented the equivalency of MSCs with pericytes. These observations lead him to speculate that “all” MSCs are derived from pericytes [11]. Similar to their

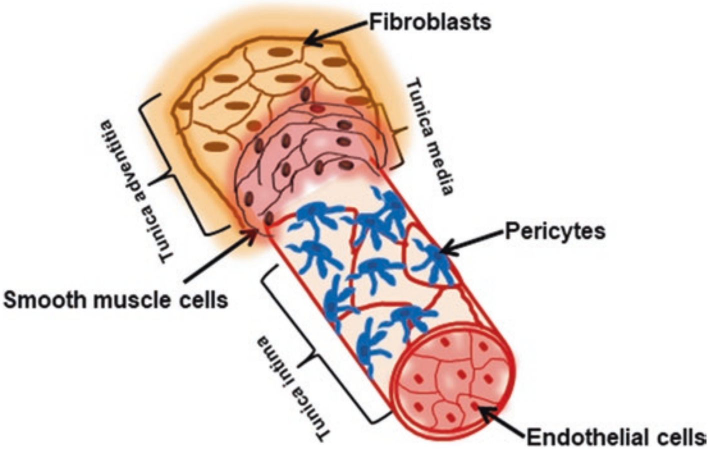

Fig. 10.1 Localization of the pericytes in the vessel

diverse morphology, expression of pericytes phenotypic markers is dynamic and changes at different developmental stages, in addition to being highly variable in different tissues and organs [63].

The production of an engineered tissue in vitro requires the use of cells to populate matrices and produce matrix resembling that of the native tissue [40]. The main successes in this field have come from the use of primary cells taken from the patient and used them with scaffolds to produce tissue for reimplantation. However, this strategy has some limitations, because of the invasive nature of cell collection and the potential for cells to be in a diseased state [40]. The use of embryonic stem cells, MSCs, fetal stem cells (umbilical cord, placenta-derived stem cells), and induced pluripotent stem cells began to become widespread after the development of stem cell field. In addition to these stem cell types, recently, pericytes have become important cell sources for tissue engineering applications [49].

Pericytes in Tissue Engineering

The term "tissue engineering" was officially used at a National Science Foundation workshop in 1988 to mean "the application of principles and methods of engineering and life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function" [52]. However, while the field of tissue engineering may be relatively new, the idea of replacing tissue with another goes as far back as the sixteenth century [50]. Tissue engineering applications consist of (1) scaffolds for providing proper three-dimensional (3D) shape of tissue construct and structural support, (2) cells for forming tissues in vitro/within the body, and (3) growth factors for signaling and determining cell fate. Evidence shows that the injected cells do not contribute to the reconstitution of the damaged tissue, highlighting the urgency of new solutions for organ/tissue replacement. Based on these considerations, clinicians and biologists are developing new techniques in the attempt to generate biological tissues "grafts" in vitro, developing the new field of tissue engineering [4]. The reconstruction of tissues can be achieved by the combination of a support material "scaffold" with cells and/or bioactive factors such as growth factors, cytokines, or chemokines (Fig. 10.2) [12, 14, 17]. The scaffold can be of natural or synthetic origin and is meant to provide support to the forming tissue and a matrix for cell retention and controlled bioactive factors release. Natural matrices are made of biologically-derived polymers, such as electrospun collagen, elastin, fibrin, fibronectin, alginates or hydrogels [12–14]. Alternatively, they can consist of entire decellularized tissues, commonly xenografts of porcine or bovine origin [39]. Conversely, synthetic matrices are composed of synthetic polymers like poly-glycolic acid, poly-lactide-co-glycolic acid (PLGA), poly-L-lactic acid, polycaprolactone, and polyurethane [17, 28, 55].

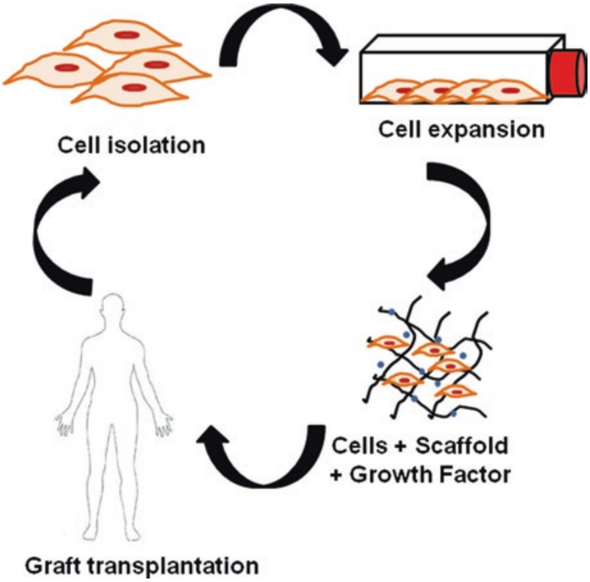

Fig. 10.2 Tissue engineering process

Pericytes in Bone Tissue Engineering

In vitro tri-lineage differentiation of pericytes into mesenchymal cell types has been well documented [32, 34]. The application of pericytes for orthopedic indications is a significant and growing field of study. Among orthopedic indications, the two most promising clinical applications are use in a bone graft substitute for spinal fusion and stimulation of fracture repair. The use of pericytes to stimulate spinal fusion has previously documented preclinical efficacy [22]. Chung et al. confirmed that implanted adipose tissue-derived human pericytes differentiated into osteoblasts and osteocytes; however, the majority of the new bone formation was of host origin. These results suggest that implanted pericytes positively regulate bone formation via direct and paracrine mechanisms [22]. Likewise, pericyte-based stimulation of fracture healing has recently shown proof of principle efficacy in an atrophic nonunion murine model [59]. Animal models of ectopic bone formation have been used to confirm the capacity for in vivo osteogenic differentiation of implanted pericytes by James et al. [42]. Pang et al. investigated mouse incisor tips as a model for the role of dental pulp stem cells in a continuous natural repair/regeneration process. They demonstrated that NG2-expressing perivascular cells (pericytes) differentiated into odontoblast-like cells and facilitated the production of reparative dentine in experimentally damaged mouse incisors [53]. Another research conducted by James et al. revealed that human adipose tissue pericytes seeded onto a PLGA scaffold increased healing of mouse critical-size calvarial defects within 2 weeks of delivery [43]. This is yet another example showing human pericytes potential in skeletal regenerative medicine.

Pericytes in Cartilage Tissue Engineering

Differentiation of stem cells to chondrocytes in vitro usually results in a heterogeneous phenotype. This is evident in the often detected overexpression of collagen type X which, in hyaline cartilage structure, is not characteristic of the mid-zone but of the deep-zone ossifying tissue [1]. In regenerative medicine, methods to better match cartilage developed in vitro to characteristic in vivo features are therefore highly desirable. The number of pericyte-specific studies in the field of cartilage and connective tissue engineering is limited. Zhang et al. co-cultured the articular chondrocytes with pericytes and adventitial cells, respectively, and showed more prominent effects on glycosaminoglycans production and collagen type II synthesis than the adventitial cells [66]. Another research, pericytes from the infrapatellar fat pad (IFP), have been investigated. These cells demonstrated increased chondrogenic potential compared with those from subcutaneous by generating more extracellular matrix (*OL2A1*, *ACAN*, and *SOX9*) than IFP MSCs [38]. The high expression of extracellular matrix by pericytes than culture-derived MSCs makes pericytes as alternative therapeutic agents for cellular therapy and regenerative medicine. It has been discussed by Wu et al. that CD146+ subpopulation represented a chondrolineage-restricted subpopulation of skeletal stem cells and may therefore act as a valuable cell source for cartilage regeneration [62]. Alakpa et al. demonstrated the phenotypic characteristics of human adipose tissue pericytes that cultured on diphenylalanine/serine peptide hydrogels with the more widely used chemical-induced method for chondrogenesis. High levels of collagen type II were noted when pericytes undergo chondrogenesis in the hydrogel without induction media. They suggested also that there was also a balanced expression of collagen relative to aggrecan production, a feature which was biased toward collagen production when cells were cultured with induction media. The study highlighted how material and chemical alterations in the cellular microenvironment have wide-ranging effects on resultant tissue type [1].

Pericytes in Dermal Tissue Engineering

Dermal tissue engineering has revolved around using different cell types for the treatment of cutaneous wounds by direct injection or scaffold-based delivery system. The process of wound healing is a complex and dynamic process involving various players for secretion of soluble mediators and deposition of extracellular matrix along with migration of various cell types, including fibroblasts, keratinocytes, macrophages, leukocytes, endothelial cells, and pericytes [9]. Human umbilical cord pericytes have recently been shown to have great potential for the treatment of skin wounds [65]. The application of human adipose-derived pericytes (alpha-smooth muscle actin (α-SMA)+, PDGFR+, NG2+, and Ang1+) on wounded skin of the rats had beneficial effects due to the increased angiogenesis, extensive collagen deposition, and reepithelialization [64]. Studies by Rajkumar et al. showed that PDGFR-β inhibition in vivo was accompanied by abnormal microvascular morphogenesis reminiscent of that observed in PDGFR-β−/− mice with significantly reduced immunostaining of the pericyte marker NG2 implying the importance of PDGFR-β signaling during the early phases of wound healing [56]. In systemic sclerosis fibrotic lesions, pericytes showed markers of activation such as PDGFR-β and high-molecular-weight melanoma-associated antigen [41]. Strong evidence showed convergence of microvascular pericytes and resident fibroblasts to a myofibroblast lineage and thereby contributing to systemic sclerosis by synthesizing excessive extracellular matrix components [46]. Laminin alpha (α) 5 (LAMA5), a subunit of the extracellular matrix component laminin-511/laminin-521 (LM-511/LM-521), promoted skin regeneration both in vitro and in vivo [54]. Analysis using immunogold localization revealed that pericytes synthesized and secreted LAMA5 in human skin. Consistent with this observation, co-culture with pericytes enhanced LM-511/LM-521 deposition in the dermal-epidermal junction of organotypic cultures [54].

Pericytes in Vascular Tissue Engineering

Platelets release various factors such as PDGF and transforming growth factor (TGF)-β that promotes pericytes detachment from endothelial cells and migration into the parenchyma. Activated pericytes can express tissue factor to promote activation of the extrinsic coagulation pathway. Platelet activation of pericytes may facilitate or regulate neovascularization. Pericytes can facilitate also angiogenesis through secretion of matrix metalloproteinases (MMPs) (driven in part by the hypoxic environment) to degrade the basement membrane allowing endothelial cells to migrate into the provisional matrix. The dissociation of pericytes from the vasculature allows for destabilization of the endothelial tube, which can promote endothelial migration and proliferation [47]. In particular, pericytes express key adhesion molecules (e.g., intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1), chemokines (e.g., human and murine C-X-C motif chemokine ligand (CXCL)-1, CXCL-8, macrophage inhibitory factor (MIF)), and receptors for proinflammatory molecules (tumor necrosis factor receptor (TNFR)-1, TNFR-II, interleukin-1 receptor (IL-1R), toll-like receptors (TLRs), NOD-like receptors) [16, 58]. In the concept of vascular tissue engineering, the secretory profile of pericytes is important.

Vascular tissue engineering approaches aim to mimic vascular layers using natural or synthetic materials with vascular cell. Current clinically approved polymer-based grafts such as Dacron and polytetrafluoroethylene have shown promising results as large vessel substitutes but perform poorly for small-diameter vessel bypass (≤6 mm) [44]. He et al. cultured human skeletal muscle pericytes with bilayered elastomeric poly(ester-urethane) urea scaffolds. The seeded scaffolds were implanted into rats as aortic interposition grafts for 8 weeks. Results showed pericytes populated the porous layer of the scaffolds and maintained their original phenotype after the dynamic culture. After implantation, pericyte-seeded vascular grafts showed a significant higher patency rate than the unseeded control [37]. Chong et al. generated biphasic vascular model containing synthetic polymer (polyacrylic acid was grafted onto biaxially-stretched polycaprolactone) seeded with human umbilical cord vein pericytes in the media layer and endothelial cells in the intima layer [21]. They reported that this construct would be suitable not only for vascular applications but for the engineering of layered tissue such as the skin, cornea, or myocardium. Synthetic scaffolds have many disadvantages, so in recent years vascular constructs made from cellularized natural scaffolds were seen to be very promising, but the number of studies comprising this area is very limited. Van der Meer et al. constructed micro-engineered 3D vascular tissue by mixing human umbilical cord vein endothelial cells (HUVECs), pericytes, and the rat tail collagen type I. This is the only study that highlights the interaction of pericytes with collagen type I as a model of vascular graft [60]. We suggested that human umbilical cord vein CD146+ pericytes may be good candidates for generating three-layered small-diameter vascular constructs when combined with human collagen type I, fibrin, elastin, dermatan sulfate, heparin, and fibronectin constituting the human natural vascular components [36]. We recently generated triple-layered vascular construct with natural human extracellular matrix proteins/glycosaminoglycans mixed with smooth muscle cells and fibroblasts differentiated from human umbilical cord vein pericytes and with HUVECs in assistance with cell sheet engineering method. For the treatment of coronary artery diseases, this vascular construct is an important step for generation of fully natural small-diameter ($\leq$5 mm) vascular graft that has the structure closest to the native blood vessel [36].

Pericytes in Cardiac Tissue Engineering

Heart failure, particularly myocardial infarction, is one of the leading causes of morbidity and mortality in the world. Stem cell transplantation therapy has emerged as a popular strategy to treat heart dysfunction. The myogenic capacity and the pro-angiogenic ability of skeletal pericytes were harnessed by organizing them in a poly-ethylene glycol hydrogel-based construct for the repair of ischemic muscle [33]. Wendel et al. produced a cardiac patch by embedded human brain pericytes and human-induced pluripotent stem cell-derived cardiomyocytes into a fibrin gel [61]. Once transplanted onto the infarcted myocardium of a rat, this pericytes/cardiomyocytes patch survived, improved cardiac function, and reduced infarct size [61]. Avolio et al. reported that cardiac pericytes seeded onto clinically approved xenograft scaffolds had penetrated into the graft and colonized after 3 weeks incubation in a bioreactor system and that cells within the graft are viable. Moreover, cells maintain the original antigenic phenotype [5]. Exploiting the paracrine activity of tissue-specific cells rather than using cells isolated from a different tissue becomes attractive for regenerative medicine. In this respect, cardiac stem cells and pericytes may be uniquely suited to produce paracrine factors instrumental to cardiac and vascular repair and regeneration [31]. Pericyte-like cells isolated and expanded from the adult saphenous vein produce large amounts of angiogenic factors such as vascular endothelial growth factor (VEGF)-A, VEGF-B, angiopoietin (Ang)-1, and miR-132, which are delivered to neighboring endothelial cells through the establishment of integrin-mediated interactions [45]. Secretion of VEGF-A, Ang-1, and miR-132 is further augmented by hypoxia, which mimics in vitro the environment encountered by cells upon transplantation into ischemic tissues [45]. Chen et al. investigated the therapeutic potential of human skeletal muscle pericytes for treating ischemic heart disease and mediating associated repair mechanisms in mice. They found that pericyte transplantation attenuates left ventricular dilatation and myocardial fibrosis and improves cardiac contractility in infarcted mouse hearts. In line with findings in saphenous vein-derived pericytes, hypoxia induced the expression of VEGF-A, PDGF-β, TGF-β1, and corresponding receptors, while expression of basic fibroblast growth factor, hepatocyte growth factor, and Ang-1 was repressed [18].

Pericytes in Blood Tissue Engineering

Hematopoietic stem cells (HSCs) are a rare subpopulation of cells residing in the bone marrow with a well-defined phenotype, lymphoid and myeloid lineage developmental potential, the capacity to reconstitute irradiated host recipients over the long-term in vivo [6]. HSC maintenance, behavior and trafficking are dependent upon information they receive from the niche in which they are localized. The concept of the niche was initially suggested after the work of Schofield and has been defined as a small functional compartment with a specific anatomical position within an organ that homes and regulates stem cell activity, quiescence, self-renewal, and differentiation for healthy tissue maintenance and repair [57]. MSCs have increasingly been implicated in HSC support as major components of the hematopoietic niche [15, 16, 30]. As pericytes were shown to be a reservoir of MSCs in vivo and in addition proximal to HSCs, recent studies have focused on their role in HSC regulation and blood tissue engineering [8]. It has been shown by Chin et al. that a subset of cells differentiated from human pluripotent stem cell defined as CD146^{hi}CD73^{hi} expressed genes associated with the hematopoietic niche and supported the maintenance of functional hematopoietic progenitors ex vivo, while CD146^{lo}CD73^{lo} cells supported differentiation. They discussed that stromal support of hematopoietic progenitors was contact dependent and mediated in part through high JAG1 expression and low WNT signaling. Molecular profiling revealed significant transcriptional similarity between human pluripotent stem cell-derived CD146++ and primary human CD146++ perivascular cells [20]. Primary immunodeficient recipients were engrafted at long-term when injected with CD45+ donor hematopoietic cells from CD146+ co-cultures and could further repopulate secondary recipients. CD146+ cells were able to activate Notch signaling in hematopoietic progenitors [23], in agreement with previous reports suggesting that Notch signaling regulates the growth and differentiation of hematopoietic progenitors via the microenvironment or niche [7].

Future Perspective

Several preclinical and clinical trials have looked at the therapeutic benefits of systemic infusion of ex vivo isolated and expanded MSCs, but there are problems with the consistency, heterogeneity, and delivery of these cells. Pericytes represent common ancestor cells giving rise to MSCs in the adult. It is clear that pericytes from a range of sources, isolated in numerous ways, and of various phenotypes, show bioengineering potential. However, lack of standardization regarding perivascular marker expression and that of their subtypes renders comparison between studies and overall conclusions difficult. Although recent publications mentioned the proteome and transcriptome profile of pericytes, these cells need to be well defined to be used clinically in the concept of the tissue engineering approach.

Conflict of Interest Statement The author declares that she has no conflicts of interest concerning this work.

Ethical Approval This article does not contain any studies with human participants or animals performed by the author.

Informed Consent This article does not contain any studies with human participants or animals performed by the author.

References

1. Alakpa EV, Jayawarna V, Burgess KEV, West CC, Peault B, Ulijn RV, Dalby MJ (2017) Improving cartilage phenotype from differentiated pericytes in tunable peptide hydrogels. Sci Rep 7:6895
2. Andreeva ER, Pugach IM, Gordon D, Orekhov AN (1998) Continuous subendothelial network formed by pericyte-like cells in human vascular bed. Tissue Cell 30:127–135
3. Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T (2016) What is a pericyte? J Cereb Blood Flow Metab 36:451–455
4. Avolio E, Alvino VV, Ghorbel MT, Campagnolo P (2017) Perivascular cells and tissue engineering: current applications and untapped potential. Pharmacol Ther 171:83–92
5. Avolio E, Rodriguez-Arabaolaza I, Spencer HL, Riu F, Mangialardi G, Slater SC, Rowlinson J, Alvino VV, Idowu OO, Soyombo S, Oikawa A, Swim MM, Kong CH, Cheng H, Jia H, Ghorbel MT, Hancox JC, Orchard CH, Angelini G, Emanueli C, Caputo M, Madeddu P (2015) Expansion and characterization of neonatal cardiac pericytes provides a novel cellular option for tissue engineering in congenital heart disease. J Am Heart Assoc 4:e002043

6. Bhattacharya D, Rossi DJ, Bryder D, Weissman IL (2006) Purified hematopoietic stem cell engraftment of rare niches corrects severe lymphoid deficiencies without host conditioning. J Exp Med 203:73–85
7. Bigas A, Robert-Moreno A, Espinosa L (2010) The notch pathway in the developing hematopoietic system. Int J Dev Biol 54:1175–1188
8. Blocki A, Wang YT, Koch M, Peh P, Beyer S, Law P, Hui J, Raghunath M (2013) Not all MSCs can act as pericytes: functional in vitro assays to distinguish pericytes from other mesenchymal stem cells in angiogenesis. Stem Cells Dev 22:2347–2355
9. Bodnar RJ, Satish L, Yates CC, Wells A (2016) Pericytes: a newly recognized player in wound healing. Wound Repair Regen 24:204–214
10. Campagnolo P, Cesselli D, Al Haj Zen A, Beltrami AP, Krankel N, Katare R, Angelini G, Emanueli C, Madeddu P (2010) Human adult vena saphena contains perivascular progenitor cells endowed with clonogenic and proangiogenic potential. Circulation 121:1735–1745
11. Caplan AI (2017) New MSC: MSCs as pericytes are sentinels and gatekeepers. J Orthop Res 35:1151–1159
12. Carneiro TN, Novaes DS, Rabelo RB, Celebi B, Chevallier P, Mantovani D, Beppu MM, Vieira RS (2013) BSA and fibrinogen adsorption on chitosan/kappa-carrageenan polyelectrolyte complexes. Macromol Biosci 13:1072–1083
13. Celebi B, Cloutier M, Balloni R, Mantovani D, Bandiera A (2012) Human elastin-based recombinant biopolymers improve mesenchymal stem cell differentiation. Macromol Biosci 12:1546–1554
14. Celebi B, Mantovani D, Pineault N (2011) Effects of extracellular matrix proteins on the growth of haematopoietic progenitor cells. Biomed Mater 6:055011
15. Celebi B, Mantovani D, Pineault N (2011) Irradiated mesenchymal stem cells improve the ex vivo expansion of hematopoietic progenitors by partly mimicking the bone marrow endosteal environment. J Immunol Methods 370:93–103
16. Celebi Saltik B, Gokcinar Yagci B (2017) Expansion of human umbilical cord blood hematopoietic progenitors with cord vein pericytes. Turk J Biol 41:49–U265
17. Celebi Saltik B, Oteyaka MO (2016) Cardiac patch design: compatibility of nanofiber materials prepared by electrospinning method with stem cells. Turk J Biol 40:510–518
18. Chen CW, Okada M, Proto JD, Gao XQ, Sekiya N, Beckman SA, Corselli M, Crisan M, Saparov A, Tobita K, Peault B, Huard J (2013) Human pericytes for ischemic heart repair. Stem Cells 31:305–316
19. Chen WC, Baily JE, Corselli M, Diaz ME, Sun B, Xiang G, Gray GA, Huard J, Peault B (2015) Human myocardial pericytes: multipotent mesodermal precursors exhibiting cardiac specificity. Stem Cells 33:557–573
20. Chin CJ, Li SW, Corselli M, Casero D, Zhu YH, Bin He C, Hardy R, Peault B, Crooks GM (2018) Transcriptionally and functionally distinct mesenchymal subpopulations are generated from human pluripotent stem cells. Stem Cell Rep 10:436–446
21. Chong MS, Chan J, Choolani M, Lee CN, Teoh SH (2009) Development of cell-selective films for layered co-culturing of vascular progenitor cells. Biomaterials 30:2241–2251
22. Chung CG, James AW, Asatrian G, Chang L, Nguyen A, Le K, Bayani G, Lee R, Stoker D, Zhang XL, Ting K, Peault B, Soo C (2014) Human perivascular stem cell-based bone graft substitute induces rat spinal fusion. Stem Cells Transl Med 3:1231–1241
23. Corselli M, Chin CJ, Parekh C, Sahaghian A, Wang W, Ge S, Evseenko D, Wang X, Montelatici E, Lazzari L, Crooks GM, Peault B (2013) Perivascular support of human hematopoietic stem/progenitor cells. Blood 121:2891–2901
24. Corselli M, Crisan M, Murray IR, West CC, Scholes J, Codrea F, Khan N, Peault B (2013) Identification of perivascular mesenchymal stromal/stem cells by flow cytometry. Cytometry A 83:714–720
25. Crisan M, Corselli M, Chen CW, Peault B (2011) Multilineage stem cells in the adult A perivascular legacy? Organogenesis 7:101–104

26. Crisan M, Corselli M, Chen WC, Peault B (2012) Perivascular cells for regenerative medicine. J Cell Mol Med 16:2851–2860
27. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, Andriolo G, Sun B, Zheng B, Zhang L, Norotte C, Teng PN, Traas J, Schugar R, Deasy BM, Badylak S, Buhring HJ, Giacobino JP, Lazzari L, Huard J, Peault B (2008) A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell 3:301–313
28. Dhandayuthapani B, Yoshida Y, Maekawa T, Kumar DS (2011) Polymeric scaffolds in tissue engineering application: a review. Int J Polym Sci 2000:1–19
29. Dore-Duffy P, Cleary K (2011) Morphology and properties of pericytes. Methods Mol Biol 686:49–68
30. Dumont N, Boyer L, Emond H, Celebi-Saltik B, Pasha R, Bazin R, Mantovani D, Roy DC, Pineault N (2014) Medium conditioned with mesenchymal stromal cell-derived osteoblasts improves the expansion and engraftment properties of cord blood progenitors. Exp Hematol 42:741–752 e1
31. Ellison-Hughes GM, Madeddu P (2017) Exploring pericyte and cardiac stem cell secretome unveils new tactics for drug discovery. Pharmacol Ther 171:1–12
32. Farrington-Rock C, Crofts NJ, Doherty MJ, Ashton BA, Griffin-Jones C, Canfield AE (2004) Chondrogenic and adipogenic potential of microvascular pericytes. Circulation 110:2226–2232
33. Fuoco C, Sangalli E, Vono R, Testa S, Sacchetti B, Latronico MV, Bernardini S, Madeddu P, Cesareni G, Seliktar D, Rizzi R, Bearzi C, Cannata SM, Spinetti G, Gargioli C (2014) 3D hydrogel environment rejuvenates aged pericytes for skeletal muscle tissue engineering. Front Physiol 5:203
34. Gokcinar-Yagci B, Ozyuncu O, Celebi-Saltik B (2016) Isolation, characterisation and comparative analysis of human umbilical cord vein perivascular cells and cord blood mesenchymal stem cells. Cell Tissue Bank 17:345–352
35. Gokcinar-Yagci B, Uckan-Cetinkaya D, Celebi-Saltik B (2015) Pericytes: properties, functions and applications in tissue engineering. Stem Cell Rev 11:549–559
36. Gokcinar-Yagci B, Yersal N, Korkusuz P, Celebi-Saltik B (2018) Generation of human umbilical cord vein CD146+ perivascular cell origined three-dimensional vascular construct. Microvasc Res 118:101–112
37. He W, Nieponice A, Soletti L, Hong Y, Gharaibeh B, Crisan M, Usas A, Peault B, Huard J, Wagner WR, Vorp DA (2010) Pericyte-based human tissue engineered vascular grafts. Biomaterials 31:8235–8244
38. Hindle P, Khan N, Biant L, Peault B (2017) The infrapatellar fat pad as a source of perivascular stem cells with increased chondrogenic potential for regenerative medicine. Stem Cells Transl Med 6:77–87
39. Hoshiba T, Lu HX, Kawazoe N, Chen GP (2010) Decellularized matrices for tissue engineering. Expert Opin Biol Ther 10:1717–1728
40. Howard D, Buttery LD, Shakesheff KM, Roberts SJ (2008) Tissue engineering: strategies, stem cells and scaffolds. J Anat 213:66–72
41. Isakson M, de Blacam C, Whelan D, McArdle A, Clover AJ (2015) Mesenchymal stem cells and cutaneous wound healing: current evidence and future potential. Stem Cells Int 2015:831095
42. James AW, Hindle P, Murray IR, West CC, Tawonsawatruk T, Shen J, Asatrian G, Zhang X, Nguyen V, Simpson AH, Ting K, Peault B, Soo C (2017) Pericytes for the treatment of orthopedic conditions. Pharmacol Ther 171:93–103
43. James AW, Zara JN, Corselli M, Askarinam A, Zhou AM, Hourfar A, Nguyen A, Megerdichian S, Asatrian G, Pang S, Stoker D, Zhang X, Wu B, Ting K, Peault B, Soo C (2012) An abundant perivascular source of stem cells for bone tissue engineering. Stem Cells Transl Med 1:673–684
44. Kannan RY, Salacinski HJ, Butler PE, Hamilton G, Seifalian AM (2005) Current status of prosthetic bypass grafts: a review. J Biomed Mater Res B Appl Biomater 74:570–581

45. Katare R, Riu F, Mitchell K, Gubernator M, Campagnolo P, Cui YX, Fortunato O, Avolio E, Cesselli D, Beltrami AP, Angelini G, Emanueli C, Madeddu P (2011) Transplantation of human pericyte progenitor cells improves the repair of infarcted heart through activation of an angiogenic program involving micro-RNA-132. Circ Res 109:894–U191
46. Koch AE, Kronfeldharrington LB, Szekanecz Z, Cho MM, Haines GK, Harlow LA, Strieter RM, Kunkel SL, Massa MC, Barr WG, Jimenez SA (1993) In-situ expression of cytokines and cellular adhesion molecules in the skin of patients with systemic-sclerosis – their role in early and late disease. Pathobiology 61:239–246
47. McDonald AG, Yang K, Roberts HR, Monroe DM, Hoffman M (2008) Perivascular tissue factor is down-regulated following cutaneous wounding: implications for bleeding in hemophilia. Blood 111:2046–2048
48. Mills SJ, Cowin AJ, Kaur P (2013) Pericytes, mesenchymal stem cells and the wound healing process. Cell 2:621–634
49. Mravic M, Asatrian G, Soo C, Lugassy C, Barnhill RL, Dry SM, Peault B, James AW (2014) From pericytes to perivascular tumours: correlation between pathology, stem cell biology, and tissue engineering. Int Orthop 38:1819–1824
50. Murphy CM, O'Brien FJ, Little DG, Schindeler A (2013) Cell-scaffold interactions in the bone tissue engineering triad. Eur Cell Mater 26:120–132
51. Nees S, Weiss DR, Senftl A, Knott M, Forch S, Schnurr M, Weyrich P, Juchem G (2012) Isolation, bulk cultivation, and characterization of coronary microvascular pericytes: the second most frequent myocardial cell type in vitro. Am J Physiol Heart Circ Physiol 302:H69–H84
52. Nerem RM (1992) Tissue engineering in the USA. Med Biol Eng Comput 30:CE8–C12
53. Pang YWY, Feng JF, Daltoe F, Fatscher R, Gentleman E, Gentleman MM, Sharpe PT (2016) Perivascular stem cells at the tip of mouse incisors regulate tissue regeneration. J Bone Miner Res 31:514–523
54. Paquet-Fifield S, Schluter H, Li A, Aitken T, Gangatirkar P, Blashki D, Koelmeyer R, Pouliot N, Palatsides M, Ellis S, Brouard N, Zannettino A, Saunders N, Thompson N, Li J, Kaur P (2009) A role for pericytes as microenvironmental regulators of human skin tissue regeneration. J Clin Investig 119:2795–2806
55. Place ES, George JH, Williams CK, Stevens MM (2009) Synthetic polymer scaffolds for tissue engineering. Chem Soc Rev 38:1139–1151
56. Rajkumar VS, Shiwen X, Bostrom M, Leoni P, Muddle J, Ivarsson M, Gerdin B, Denton CP, Bou-Gharios G, Black CM, Abraham DJ (2006) Platelet-derived growth factor-beta receptor activation is essential for fibroblast and pericyte recruitment during cutaneous wound healing. Am J Pathol 169:2254–2265
57. Scadden DT (2006) The stem-cell niche as an entity of action. Nature 441:1075–1079
58. Stark K, Eckart A, Haidari S, Tirniceriu A, Lorenz M, von Bruhl ML, Gartner F, Khandoga AG, Legate KR, Pless R, Hepper I, Lauber K, Walzog B, Massberg S (2013) Capillary and arteriolar pericytes attract innate leukocytes exiting through venules and 'instruct' them with pattern-recognition and motility programs. Nat Immunol 14:41–51
59. Tawonsawatruk T, West CC, Murray IR, Soo C, Peault B, Simpson AH (2016) Adipose derived pericytes rescue fractures from a failure of healing – non-union. Sci Rep 6:22779
60. van der Meer AD, Orlova VV, ten Dijke P, van den Berg A, Mummery CL (2013) Three-dimensional co-cultures of human endothelial cells and embryonic stem cell-derived pericytes inside a microfluidic device. Lab Chip 13:3562–3568
61. Wendel JS, Ye L, Tao R, Zhang J, Zhang J, Kamp TJ, Tranquillo RT (2015) Functional effects of a tissue-engineered cardiac patch from human induced pluripotent stem cell-derived cardiomyocytes in a rat infarct model. Stem Cells Transl Med 4:1324–1332
62. Wu YX, Jing XZ, Sun Y, Ye YP, Guo JC, Huang JM, Xiang W, Zhang JM, Guo FJ (2017) CD146+ skeletal stem cells from growth plate exhibit specific chondrogenic differentiation capacity in vitro. Mol Med Rep 16:8019–8028
63. Xu JG, Gong T, Heng BC, Zhang CF (2017) A systematic review: differentiation of stem cells into functional pericytes. FASEB J 31:1775–1786

64. Zamora DO, Natesan S, Becerra S, Wrice N, Chung E, Suggs LJ, Christy RJ (2013) Enhanced wound vascularization using a dsASCs seeded FPEG scaffold. Angiogenesis 16:745–757
65. Zebardast N, Lickorish D, Davies JE (2010) Human umbilical cord perivascular cells (HUCPVC): a mesenchymal cell source for dermal wound healing. Organogenesis 6:197–203
66. Zhang S, Ba K, Wu L, Lee S, Peault B, Petrigliano FA, McAllister DR, Adams JS, Evseenko D, Lin Y (2015) Adventitial cells and perictyes support chondrogenesis through different mechanisms in 3-dimensional cultures with or without nanoscaffolds. J Biomed Nanotechnol 11:1799–1807